FIG. 1

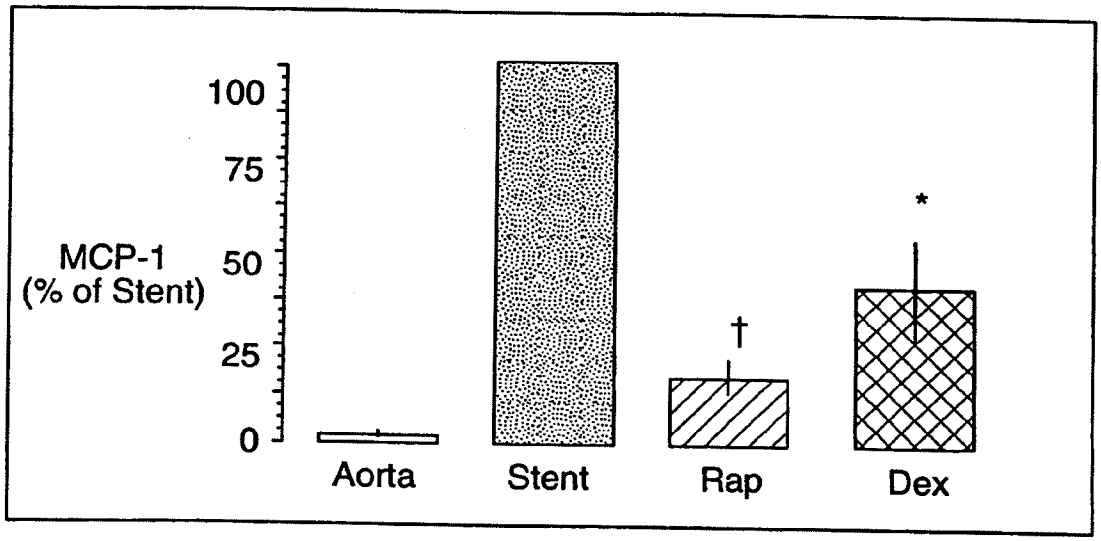


FIG. 2

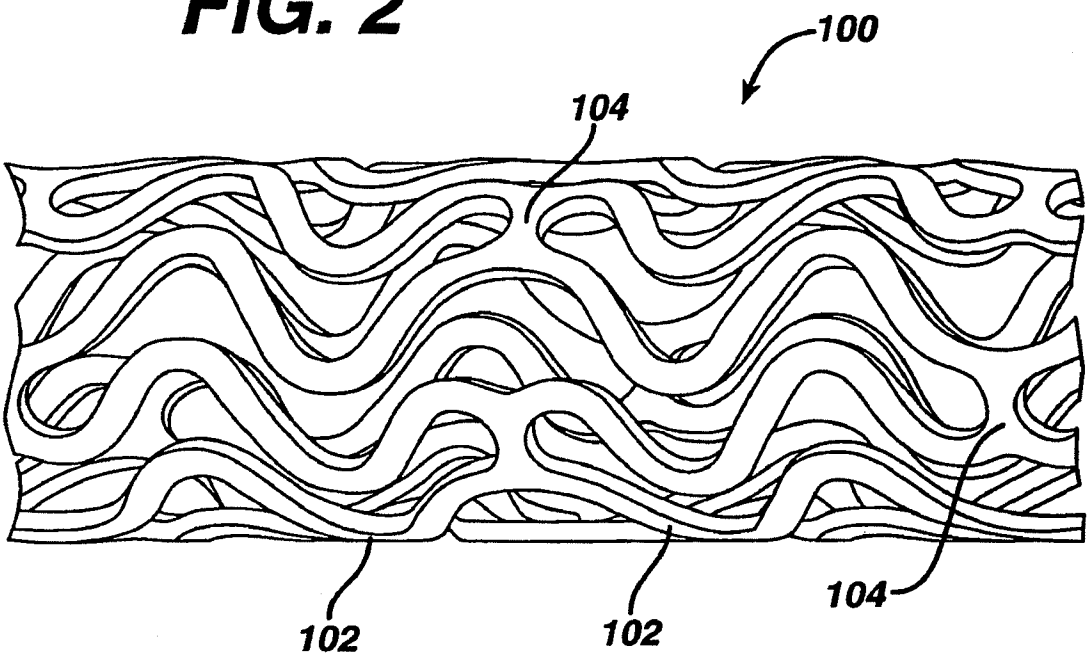
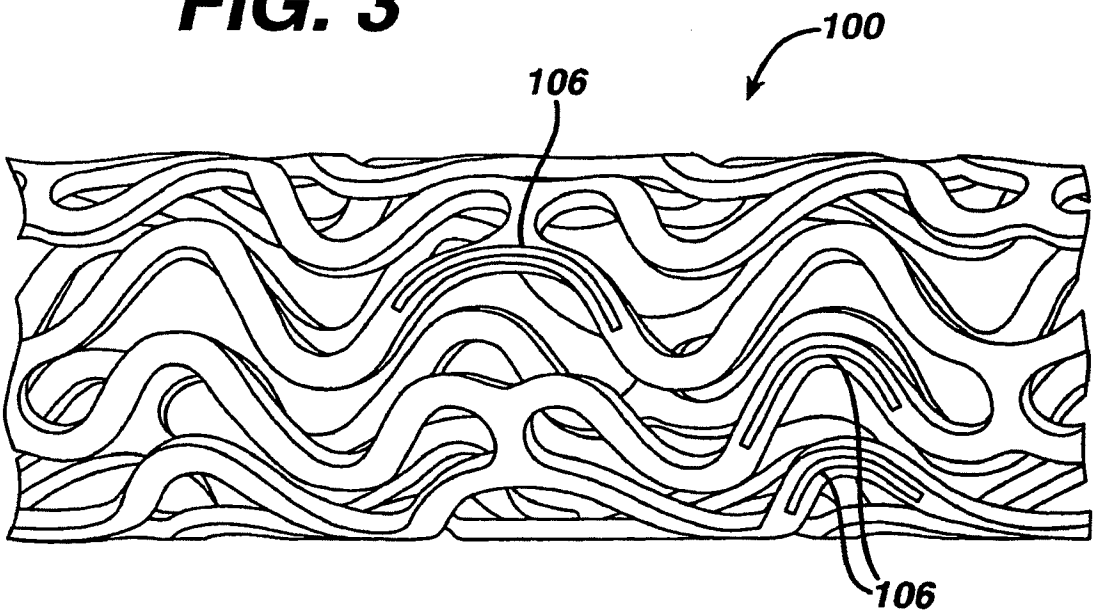



FIG. 3



# DRUG/DRUG DELIVERY SYSTEMS FOR THE PREVENTION AND TREATMENT OF VASCULAR DISEASE

## CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 09/850,293, filed May 7, 2001, now abandoned, which in turn claims priority of U.S. Provisional Application No. 60/263,979, filed Jan. 25, 2001, U.S. Provisional Application No. 60/263,806, filed January 24, 2001, U.S. Provisional Application No. 60/262,614, filed Jan. 18, 2001, U.S. Provisional Application No. 60/262,461, filed Jan. 18, 2001, and is a continuation-in-part of U.S. Application No. 09,575,480, filed May 19, 2000, now pending, which in turn claims priority of U.S. Provisional Application No. 60/204,4 17, filed May 12, 2000.

## BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to drugs and drug delivery systems for the prevention and treatment of vascular disease, and more particularly to drugs and drug delivery systems for the prevention and treatment of neointimal hyperplasia.

2. Discussion of the Related Art

Many individuals suffer from circulatory disease caused by a progressive blockage of the blood vessels that perfuse the heart and other major organs with nutrients. More severe blockage of blood vessels in such individuals often leads to hypertension, ischemic injury, stroke, or myocardial infarction. Atherosclerotic lesions, which limit or obstruct coronary blood flow, are the major cause of ischemic heart disease. Percutaneous transluminal coronary angioplasty is a medical procedure whose purpose is to increase blood flow through an artery. Percutaneous transluminal coronary angioplasty is the predominant treatment for coronary vessel stenosis. The increasing use of this procedure is attributable to its relatively high success rate and its minimal invasiveness compared with coronary bypass surgery. A limitation associated with percutaneous transluminal coronary angioplasty is the abrupt closure of the vessel which may occur immediately after the procedure and restenosis which occurs gradually following the procedure. Additionally, restenosis is a chronic problem in patients who have undergone saphenous vein bypass grafting. The mechanism of acute occlusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets and fibrin along the damaged length of the newly opened blood vessel.

Restenosis after percutaneous transluminal coronary angioplasty is a more gradual process initiated by vascular injury. Multiple processes, including thrombosis, inflammation, growth factor and cytokine release, cell proliferation, cell migration and extracellular matrix synthesis each contribute to the restenotic process.

While the exact mechanism of restenosis is not completely understood, the general aspects of the restenosis process have been identified. In the normal arterial wall, smooth muscle cells proliferate at a low rate, approximately less than 0.1 percent per day. Smooth muscle cells in the vessel walls exist in a contractile phenotype characterized by eighty to ninety percent of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, Golgi, and free ribosomes are few and are located in the perinuclear region. Extracellular matrix surrounds the



smooth muscle cells and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining smooth muscle cells in the contractile phenotypic state (Campbell and Campbell, 1985).

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the vessel wall become injured, initiating a thrombotic and inflammatory response. Cell derived growth factors such as platelet derived growth factor, fibroblast growth factor, epidermal growth factor, thrombin, etc., released from platelets, invading macrophages and/or leukocytes, or directly from the smooth muscle cells provoke proliferative and migratory responses in medial smooth muscle cells. These cells undergo a change from the contractile phenotype to a synthetic phenotype characterized by only a few contractile filament bundles, extensive rough endoplasmic reticulum, Golgi and free ribosomes. Proliferation/migration usually begins within one to two days post-injury and peaks several days thereafter (Campbell and Campbell, 1987; Clowes and Schwartz, 1985).

Daughter cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate and secrete significant amounts of extracellular matrix proteins. Proliferation, migration and extracellular matrix synthesis continue until the damaged endothelial layer is repaired at which time proliferation slows within the intima, usually within seven to fourteen days post-injury. The newly formed tissue is called neointima. The further vascular narrowing that occurs over the next three to six months is due primarily to negative or constrictive remodeling.

Simultaneous with local proliferation and migration, inflammatory cells invade the site of vascular injury. Within three to seven days post-injury, inflammatory cells have migrated to the deeper layers of the vessel wall. In animal models employing either balloon injury or stent implantation, inflammatory cells may persist at the site of vascular injury for at least thirty days (Tanaka et al., 1993; Edelman et al., 1998). Inflammatory cells therefore are present and may contribute to both the acute and chronic phases of restenosis.

Numerous agents have been examined for presumed anti-proliferative actions in restenosis and have shown some activity in experimental animal models. Some of the agents which have been shown to successfully reduce the extent of intimal hyperplasia in animal models include: heparin and heparin fragments (Clowes, A. W. and Karnovsky M., Nature 265: 25-26, 1977; Guyton, J. R. et al., Circ. Res., 46: 625-634, 1980; Clowes, A. W. and Clowes, M. M., Lab. Invest. 52: 611-616, 1985; Clowes, A. W. and Clowes, M. M., Circ. Res. 58: 839-845, 1986; Majesky et al., Circ. Res. 61: 296-300, 1987; Snow et al., Am. J. Pathol. 137: 313-330, 1990; Okada, T. et al., Neurosurgery 25: 92-98, 1989), colchicine (Currier, J. W. et al., Circ. 80: 11-66, 1989), taxol (Sollot, S. J. et al., J. Clin. Invest. 95: 1869-1876, 1995), angiotensin converting enzyme (ACE) inhibitors (Powell, J. S. et al., Science, 245: 186-188, 1989), angiopeptin (Lundergan, C. F. et al. Am. J. Cardiol. 17(Suppl. B):132B-136B, 1991), cyclosporin A (Jonasson, L. et al., Proc. Natl., Acad. Sci., 85: 2303, 1988), goat-anti-rabbit PDGF antibody (Ferns, G. A. A., et al., Science 253: 1129-1132, 1991), terbinafine (Nemecek, G. M. et al., J. Pharmacol. Exp. Thera. 248: 1167-1174, 1989), trapidil (Liu, M. W. et al., Circ. 81: 1089-1093, 1990), tranilast (Fukuyama, J. et al., Eur. J. Pharmacol. 318: 327-332, 1996), interferon-gamma (Hansson, G. K. and Holm, J., Circ. 84: 1266-1272, 1991), rapamycin (Marx, S. O. et al., Circ. Res. 76: 412-417, 1995), corticosteroids (Colburn, M. D. et al., J. Vasc. Surg. 15:

510-518, 1992), see also Berk, B. C. et al., J. Am. Coll. Cardiol. 17: 111B-117B, 1991), ionizing radiation (Weinberger, J. et al., Int. J. Rad. Onc. Biol. Phys. 36: 767-775, 1996), fusion toxins (Farb, A. et al., Circ. Res. 80: 542-550, 1997) antisense oligonucleotides (Simons, M. et al., Nature 359: 67-70, 1992) and gene vectors (Chang, M. W. et al., J. Clin. Invest. 96: 2260-2268, 1995). Anti-proliferative effects on smooth muscle cells in vitro have been demonstrated for many of these agents, including heparin and heparin conjugates, taxol, tranilast, colchicine, ACE inhibitors, fusion toxins, antisense oligonucleotides, rapamycin and ionizing radiation. Thus, agents with diverse mechanisms of smooth muscle cell inhibition may have therapeutic utility in reducing intimal hyperplasia.

However, in contrast to animal models, attempts in human angioplasty patients to prevent restenosis by systemic pharmacologic means have thus far been unsuccessful. Neither aspirin-dipyridamole, ticlopidine, anti-coagulant therapy (acute heparin, chronic warfarin, hirudin or hirulog), thromboxane receptor antagonism nor steroids have been effective in preventing restenosis, although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty (Mak and Topol, 1997; Lang et al., 1991; Popma et al., 1991). The platelet GP IIb/IIIa receptor, antagonist, Reopro is still under study but has not shown promising results for the reduction in restenosis following angioplasty and stenting. Other agents, which have also been unsuccessful in the prevention of restenosis, include the calcium channel antagonists, prostacyclin mimetics, angiotensin converting enzyme inhibitors, serotonin receptor antagonists, and anti-proliferative agents. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; anti-proliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Mak and Topol, 1997; Lang et al., 1991; Popma et al., 1991).

Additional clinical trials in which the effectiveness for preventing restenosis utilizing dietary fish oil supplements or cholesterol lowering agents has been examined showing either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Mak and Topol, 1997; Franklin and Faxon, 1993: Serruys, P. W. et al., 1993). Recent observations suggest that the antilipid/antioxidant agent, probucol may be useful in preventing restenosis but this work requires confirmation (Tardif et al., 1997; Yokoi, et al., 1997). Probucol is presently not approved for use in the United States and a thirty-day pretreatment period would preclude its use in emergency angioplasty. Additionally, the application of ionizing radiation has shown significant promise in reducing or preventing restenosis after angioplasty in patients with stents (Teirstein et al., 1997). Currently, however, the most effective treatments for restenosis are repeat angioplasty, atherectomy or coronary artery bypass grafting, because no therapeutic agents currently have Food and Drug Administration approval for use for the prevention of post-angioplasty restenosis.

Unlike systemic pharmacologic therapy, stents have proven effective in significantly reducing restenosis. Typically, stents are balloon-expandable slotted metal tubes (usually, but not limited to, stainless steel), which, when expanded within the lumen of an angioplastied coronary artery, provide structural support through rigid scaffolding to the arterial wall. This support is helpful in maintaining vessel lumen patency. In two randomized clinical trials,



stents increased angiographic success after percutaneous transluminal coronary angioplasty, by increasing minimal lumen diameter and reducing, but not eliminating, the incidence of restenosis at six months (Serruys et al., 1994; Fischman et al., 1994).

Additionally, the heparin coating of stents appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al., 1996). Thus, sustained mechanical expansion of a stenosed coronary artery with a stent has been shown to provide some measure of restenosis prevention, and the coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs locally, at the site of injured tissue.

Accordingly, there exists a need for effective drugs and drug delivery systems for the effective prevention and treatment of neointimal thickening that occurs after percutaneous transluminal coronary angioplasty and stent implantation.

## SUMMARY OF THE INVENTION

The drugs and drug delivery systems of the present invention provide a means for overcoming the difficulties associated with the methods and devices currently in use as briefly described above.

In accordance with one aspect, the present invention is directed to a method for the prevention of constrictive remodeling. The method comprises the controlled delivery, by release from an intraluminal medical device, of a compound in therapeutic dosage amounts.

In accordance with another aspect, the present invention is directed to a drug delivery device. The drug delivery device comprises an intraluminal medical device and a therapeutic dosage of an agent releasably affixed to the intraluminal medical device for the treatment of constrictive vascular remodeling.

The drugs and drug delivery systems of the present invention utilize a stent or graft in combination with rapamycin or other drugs/agents/compounds to prevent and treat neointimal hyperplasia, i.e. restenosis, following percutaneous transluminal coronary angioplasty and stent implantation. It has been determined that rapamycin functions to inhibit smooth muscle cell proliferation through a number of mechanisms. It has also been determined that rapamycin eluting stent coatings produce superior effects in humans, when compared to animals, with respect to the magnitude and duration of the reduction in neointimal hyperplasia. Rapamycin administration from a local delivery platform also produces an anti-inflammatory effect in the vessel wall that is distinct from and complimentary to its smooth muscle cell anti-proliferative effect. In addition, it has also been demonstrated that rapamycin inhibits constrictive vascular remodeling in humans.

Other drugs, agents or compounds which mimic certain actions of rapamycin may also be utilized in combination with local delivery systems or platforms.

The local administration of drugs, agents or compounds to stented vessels have the additional therapeutic benefit of higher tissue concentration than that which would be achievable through the systemic administration of the same drugs, agents or compounds. Other benefits include reduced systemic toxicity, single treatment, and ease of administration. An additional benefit of a local delivery device and drug, agent or compound therapy may be to reduce the dose of the therapeutic drugs, agents or compounds and thus limit their toxicity, while still achieving a reduction in restenosis.

## BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other features and advantages of the invention will be apparent from the following, more particular description of preferred embodiments of the invention, as illustrated in the accompanying drawings.

FIG. **1** is a chart indicating the effectiveness of rapamycin as an anti-inflammatory relative to other anti-inflammatories.

FIG. **2** is a view along the length of a stent (ends not shown) prior to expansion showing the exterior surface of the stent and the characteristic banding pattern.

FIG. **3** is a perspective view of the stent of FIG. **1** having reservoirs in accordance with the present invention.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As stated above, the proliferation of vascular smooth muscle cells in response to mitogenic stimuli that are released during balloon angioplasty and stent implantation is the primary cause of neointimal hyperplasia. Excessive neointimal hyperplasia can often lead to impairment of blood flow, cardiac ischemia and the need for a repeat intervention in selected patients in high risk treatment groups. Yet repeat revascularization incurs risk of patient morbidity and mortality while adding significantly to the cost of health care. Given the widespread use of stents in interventional practice, there is a clear need for safe and effective inhibitors of neointimal hyperplasia.

Rapamycin is a macroyclic triene antibiotic produced by streptomyces hygroscopicus as disclosed in U.S. Pat. No. 3,929,992. It has been found that rapamycin inhibits the proliferation of vascular smooth muscle cells in vivo. Accordingly, rapamycin may be utilized in treating intimal smooth muscle cell hyperplasia, restenosis and vascular occlusion in a mammal, particularly following either biologically or mechanically mediated vascular injury, or under conditions that would predispose a mammal to suffering such a vascular injury. Rapamycin functions to inhibit smooth muscle cell proliferation and does not interfere with the re-endothelialization of the vessel walls.

Rapamycin functions to inhibit smooth muscle cell proliferation through a number of mechanisms. In addition, rapamycin reduces the other effects caused by vascular injury, for example, inflammation. The operation and various functions of rapamycin are described in detail below. Rapamycin as used throughout this application shall include rapamycin, rapamycin analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

Rapamycin reduces vascular hyperplasia by antagonizing smooth muscle proliferation in response to mitogenic signals that are released during angioplasty. Inhibition of growth factor and cytokine mediated smooth muscle proliferation at the late G1 phase of the cell cycle is believed to be the dominant mechanism of action of rapamycin. However, rapamycin is also known to prevent T-cell proliferation and differentiation when administered systemically. This is the basis for its immunosuppresive activity and its ability to prevent graft rejection.

The molecular events that are responsible for the actions of rapamycin, a known anti-proliferative, which acts to reduce the magnitude and duration of neointimal hyperplasia, are still being elucidated. It is known, however, that rapamycin enters cells and binds to a high-affinity cytosolic protein called FKBP12. The complex of rapamycin and



FKPB12 in turn binds to and inhibits a phosphoinositide (PI)-3 kinase called the "mammalian Target of Rapamycin" or TOR. TOR is a protein kinase that plays a key role in mediating the downstream signaling events associated with mitogenic growth factors and cytokines in smooth muscle cells and T lymphocytes. These events include phosphorylation of p27, phosphorylation of p70 s6 kinase and phosphorylation of 4BP-1, an important regulator of protein translation.

It is recognized that rapamycin reduces restenosis by inhibiting neointimal hyperplasia. However, there is evidence that rapamycin may also inhibit the other major component of restenosis, namely, negative remodeling. Remodeling is a process whose mechanism is not clearly understood but which results in shrinkage of the external elastic lamina and reduction in lumenal area over time, generally a period of approximately three to six months in humans.

Negative or constrictive vascular remodeling may be quantified angiographically as the percent diameter stenosis at the lesion site where there is no stent to obstruct the process. If late lumen loss is abolished in-lesion, it may be inferred that negative remodeling has been inhibited. Another method of determining the degree of remodeling involves measuring in-lesion external elastic lamina area using intravascular ultrasound (IVUS). Intravascular ultrasound is a technique that can image the external elastic lamina as well as the vascular lumen. Changes in the external elastic lamina proximal and distal to the stent from the post-procedural timepoint to four-month and twelve-month follow-ups are reflective of remodeling changes.

Evidence that rapamycin exerts an effect on remodeling comes from human implant studies with rapamycin coated stents showing a very low degree of restenosis in-lesion as well as in-stent. In-lesion parameters are usually measured approximately five millimeters on either side of the stent i.e. proximal and distal. Since the stent is not present to control remodeling in these zones which are still affected by balloon expansion, it may be inferred that rapamycin is preventing vascular remodeling.

The data in Table 1 below illustrate that in-lesion percent diameter stenosis remains low in the rapamycin treated groups, even at twelve months. Accordingly, these results support the hypothesis that rapamycin reduces remodeling.

TABLE 1.0

Angiographic In-Lesion Percent Diameter Stenosis (%, mean ± SD and "n=") In Patients Who Received a Rapamycin-Coated Stent

| Coating Group | Post Placement | 4–6 month Follow Up | 12 month Follow Up |
|---|---|---|---|
| Brazil | 10.6 ± 5.7 (30) | 13.6 ± 8.6 (30) | 22.3 ± 7.2 (15) |
| Netherlands | 14.7 ± 8.8 | 22.4 ± 6.4 | — |

Additional evidence supporting a reduction in negative remodeling with rapamycin comes from intravascular ultrasound data that was obtained from a first-in-man clinical program as illustrated in Table 2 below.

TABLE 2.0

Matched IVUS data in Patients Who Received a Rapamycin-Coated Stent

| IVUS Parameter | Post (n=) | 4-Month Follow-Up (n=) | 12-Month Follow-Up (n=) |
|---|---|---|---|
| Mean proximal vessel area ($mm^2$) | 16.53 ± 3.53 (27) | 16.31 ± 4.36 (28) | 13.96 ± 2.26 (13) |
| Mean distal vessel area ($mm^2$) | 13.12 ± 3.68 (26) | 13.53 ± 4.17 (26) | 12.49 ± 3.25 (14) |

The data illustrated that there is minimal loss of vessel area proximally or distally which indicates that inhibition of negative remodeling has occurred in vessels treated with rapamycin-coated stents.

Other than the stent itself, there have been no effective solutions to the problem of vascular remodeling. Accordingly, rapamycin may represent a biological approach to controlling the vascular remodeling phenomenon.

It may be hypothesized that rapamycin acts to reduce negative remodeling in several ways. By specifically blocking the proliferation of fibroblasts in the vascular wall in response to injury, rapamycin may reduce the formation of vascular scar tissue. Rapamycin may also affect the translation of key proteins involved in collagen formation or metabolism.

Rapamycin used in this context includes rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

In a preferred embodiment, the rapamycin is delivered by a local delivery device to control negative remodeling of an arterial segment after balloon angioplasty as a means of reducing or preventing restenosis. While any delivery device may be utilized, it is preferred that the delivery device comprises a stent that includes a coating or sheath which elutes or releases rapamycin. The delivery system for such a device may comprise a local infusion catheter that delivers rapamycin at a rate controlled by the administrator.

Rapamycin may also be delivered systemically using an oral dosage form or a chronic injectible depot form or a patch to deliver rapamycin for a period ranging from about seven to forty-five days to achieve vascular tissue levels that are sufficient to inhibit negative remodeling. Such treatment is to be used to reduce or prevent restenosis when administered several days prior to elective angioplasty with or without a stent.

Data generated in porcine and rabbit models show that the release of rapamycin into the vascular wall from a nonerodible polymeric stent coating in a range of doses (35-430 ug/5-18 mm coronary stent) produces a peak fifty to fifty-five percent reduction in neointimal hyperplasia as set forth in Table 3 below. This reduction, which is maximal at about twenty-eight to thirty days, is typically not sustained in the range of ninety to one hundred eighty days in the porcine model as set forth in Table 4 below.

TABLE 3.0

Animal Studies with Rapamycin-coated stents. Values are mean ± Standard Error of Mean

| Study | Duration | Stent[1] | Rapamycin | N | Neointimal Area ($mm^2$) | % Change From Polyme | % Change From Metal |
|---|---|---|---|---|---|---|---|
| Porcine | | | | | | | |
| 98009 | 14 days | Metal | | 8 | 2.04 ± 0.17 | | |
| | | 1X + rapamycin | 153 µg | 8 | 1.66 ± 0.17* | -42% | -19% |
| | | 1X + TC300 + rapamycin | 155 µg | 8 | 1.51 ± 0.19* | -47% | -26% |
| 99005 | 28 days | Metal | | 10 | 2.29 ± 0.21 | | |
| | | | | 9 | 3.91 ± 0.60** | | |
| | | 1X + TC30 + rapamycin | 130 µg | 8 | 2.81 ± 0.34 | | +23% |
| | | 1X + TC100 + rapamycin | 120 µg | 9 | 2.62 ± 0.21 | | +14% |
| 99006 | 28 days | Metal | | 12 | 4.57 ± 0.46 | | |
| | | EVA/BMA 3X | | 12 | 5.02 ± 0.62 | | +10% |
| | | 1X + rapamycin | 125 µg | 11 | 2.84 ± 0.31* ** | -43% | -38% |
| | | 3X + rapamycin | 430 µg | 12 | 3.06 ± 0.17* ** | -39% | -33% |
| | | 3X + rapamycin | 157 µg | 12 | 2.77 ± 0.41* ** | -45% | -39% |
| 99011 | 28 days | Metal | | 11 | 3.09 ± 0.27 | | |
| | | | | 11 | 4.52 ± 0.37 | | |
| | | 1X + rapamycin | 189 µg | 14 | 3.05 ± 0.35 | | -1% |
| | | 3X + rapamycin/dex | 182/363 µg | 14 | 2.72 ± 0.71 | | -12% |
| 99021 | 60 days | Metal | | 12 | 2.14 ± 0.25 | | |
| | | 1X + rapamycin | 181 µg | 12 | 2.95 ± 0.38 | | +38% |
| 99034 | 28 days | Metal | | 8 | 5.24 ± 0.58 | | |
| | | 1X + rapamycin | 186 µg | 8 | 2.47 ± 0.33** | | -53% |
| | | 3X + rapamycin/dex | 185/369 µg | 6 | 2.42 ± 0.64** | | -54% |
| 20001 | 28 days | Metal | | 6 | 1.81 ± 0.09 | | |
| | | 1X + rapamycin | 172 µg | 5 | 1.66 ± 0.44 | | -8% |
| 20007 | | | | | | | |
| | 30 days | Metal | | 9 | 2.94 ± 0.43 | | |
| | | 1XTC + rapamycin | 155 µg | 10 | 1.40 ± 0.11* | | -52%* |
| Rabbit | | | | | | | |
| 99019 | 28 days | Metal | | 8 | 1.20 ± 0.07 | | |

TABLE 3.0-continued

Animal Studies with Rapamycin-coated stents.
Values are mean ± Standard Error of Mean

| Study | Duration | Stent[1] | Rapamycin | N | Neointimal Area ($mm^2$) | % Change From Polyme | % Change From Metal |
|---|---|---|---|---|---|---|---|
| | | EVA/BMA 1X | | 10 | 1.26 ± 0.16 | | +5% |
| | | 1X + rapamycin | 64 μg | 9 | 0.92 ± 0.14 | −27% | −23% |
| | | 1X + rapamycin | 196 μg | 10 | 0.66 ± 0.12* ** | −48% | −45% |
| 99020 | 28 days | Metal | | 12 | 1.18 ± 0.10 | | |
| | | EVA/BMA 1X + rapamycin | 197 μg | 8 | 0.81 ± 0.16 | | −32% |

[1]Stent nomenclature: EVA/BMA 1X, 2X, and 3X signifies approx. 500 μg, 1000 μg, and 1500 μg total mass (polymer + drug), respectively. TC, top coat of 30 μg, 100 μg, or 300 μg drug-free BMA; Biphasic; 2 × 1X layers of rapamycin in EVA/BMA spearated by a 100 μg drug-free BMA layer.
[2]0.25 mg/kg/d × 14 d preceeded by a loading dose of 0.5 mg/kg/d × 3 d prior to stent implantation.
*p < 0.05 from EVA/BMA control.
**p < 0.05 from Metal;
#Inflammation score: (0 = essentially no intimal involvement; 1 = <25% intima involved; 2 =≧25% intima involved; 3 = >50% intima involved).

TABLE 4.0

180 day Porcine Study with Rapamycin-coated stents.
Values are mean ± Standard Error of Mean

| Study | Duration | Stent[1] | Rapamycin | N | Neointimal Area ($mm^2$) | % Change From Polyme | % Change From Metal | Inflammation Score # |
|---|---|---|---|---|---|---|---|---|
| 20007 | 3 days | Metal | | 10 | 0.38 ± 0.06 | | | 1.05 ± 0.06 |
| (ETP-2-002233-P) | | 1XTC + rapamycin | 155 μg | 10 | 0.29 ± 0.03 | | −24% | 1.08 ± 0.04 |
| | 30 days | Metal | | 9 | 2.94 ± 0.43 | | | 0.11 ± 0.08 |
| | | 1XTC + rapamycin | 155 μg | 10 | 1.40 ± 0.11* | | −52%* | 0.25 ± 0.10 |
| | 90 days | Metal | | 10 | 3.45 ± 0.34 | | | 0.20 ± 0.08 |
| | | 1XTC + rapamycin | 155 μg | 10 | 3.03 ± 0.29 | | −12% | 0.80 ± 0.23 |
| | | 1X + rapamycin | 171 μg | 10 | 2.86 ± 0.35 | | −17% | 0.60 ± 0.23 |
| | 180 days | Metal | | 10 | 3.65 ± 0.39 | | | 0.65 ± 0.21 |
| | | 1XTC + rapamycin | 155 μg | 10 | 3.34 ± 0.31 | | −8% | 1.50 ± 0.34 |
| | | 1X + rapamycin | 171 μg | 10 | 3.87 ± 0.28 | | +6% | 1.68 ± 0.37 |

The release of rapamycin into the vascular wall of a human from a nonerodible polymeric stent coating provides superior results with respect to the magnitude and duration of the reduction in neointimal hyperplasia within the stent as compared to the vascular walls of animals as set forth above.

Humans implanted with a rapamycin coated stent comprising rapamycin in the same dose range as studied in animal models using the same polymeric matrix, as described above, reveal a much more profound reduction in neointimal hyperplasia than observed in animal models, based on the magnitude and duration of reduction in neointima. The human clinical response to rapamycin reveals essentially total abolition of neointimal hyperplasia inside the stent using both angiographic and intravascular ultrasound measurements. These results are sustained for at least one year as set forth in Table 5 below.

TABLE 5.0

Patients Treated (N = 45 patients) with a Rapamycin-coated Stent

| Effectiveness Measures | Sirolimus FIM (N = 45 Patients, 45 Lesions) | 95% Confidence Limit |
|---|---|---|
| Procedure Success (QCA) | 100.0% (45/45) | [92.1%, 100.0%] |
| 4-month In-Stent Diameter Stenosis (%) | | |
| Mean ± SD (N) | 4.8% ± 6.1% (30) | [2.6%, 7.0%] |
| Range (min, max) | (−8.2%, 14.9%) | |
| 6-month In-Stent Diameter Stenosis (%) | | |
| Mean ± SD (N) | 8.9% ± 7.6% (13) | [4.8%, 13.0%] |
| Range (min, max) | (−2.9%, 20.4%) | |
| 12-month In-Stent Diameter Stenosis (%) | | |
| Mean ± SD (N) | 8.9% ± 6.1% (15) | [5.8%, 12.0%] |
| Range (min, max) | (−3.0%, 22.0%) | |

TABLE 5.0-continued

| Patients Treated (N = 45 patients) with a Rapamycin-coated Stent | | |
|---|---|---|
| Effectiveness Measures | Sirolimus FIM (N = 45 Patients, 45 Lesions) | 95% Confidence Limit |
| 4-month In-Stent Late Loss (mm) | | |
| Mean ± SD (N) | 0.00 ± 0.29 (30) | [−0.10, 0.10] |
| Range (min, max) | (−0.51, 0.45) | |
| 6-month In-Stent Late Loss (mm) | | |
| Mean ± SD (N) | 0.25 ± 0.27 (13) | [0.10, 0.39] |
| Range (min, max) | (−0.51, 0.91) | |
| 12-month In-Stent Late Loss (mm) | | |
| Mean ± SD (N) | 0.11 ± 0.36 (15) | [−0.08, 0.29] |
| Range (min, max) | (−0.51, 0.82) | |
| 4-month Obstruction Volume (%) (IVUS) | | |
| Mean ± SD (N) | 10.48% ± 2.78% (28) | [9.45%, 11.51%] |
| Range (min, max) | (4.60%, 16.35%) | |
| 6-month Obstruction Volume (%) (IVUS) | | |
| Mean ± SD (N) | 7.22% ± 4.60% (13) | [4.72%, 9.72%], |
| Range (min, max) | (3.82%, 19.88%) | |
| 12-month Obstruction Volume (%) (IVUS) | | |
| Mean ± SD (N) | 2.11% ± 5.28% (15) | [0.00%, 4.78%], |
| Range (min, max) | (0.00%, 19.89%) | |
| 6-month Target Lesion Revascularization (TLR) | 0.0% (0/30) | [0.0%, 9.5%] |
| 12-month Target Lesion Revascularization (TLR) | 0.0% (0/15) | [0.0%, 18.1%] |

QCA = Quantitative Coronary Angiography
SD = Standard Deviation
IVUS = Intravascular Ultrasound

Rapamycin produces an unexpected benefit in humans when delivered from a stent by causing a profound reduction in in-stent neointimal hyperplasia that is sustained for at least one year. The magnitude and duration of this benefit in humans is not predicted from animal model data. Rapamycin used in this context includes rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

These results may be due to a number of factors. For example, the greater effectiveness of rapamycin in humans is due to greater sensitivity of its mechanism(s) of action toward the pathophysiology of human vascular lesions compared to the pathophysiology of animal models of angioplasty. In addition, the combination of the dose applied to the stent and the polymer coating that controls the release of the drug is important in the effectiveness of the drug.

As stated above, rapamycin reduces vascular hyperplasia by antagonizing smooth muscle proliferation in response to mitogenic signals that are released during angioplasty injury. Also, it is known that rapamycin prevents T-cell proliferation and differentiation when administered systemically. It has also been determined that rapamycin exerts a local inflammatory effect in the vessel wall when administered from a stent in low doses for a sustained period of time (approximately two to six weeks). The local anti-inflammatory benefit is profound and unexpected. In combination with the smooth muscle anti-proliferative effect, this dual mode of action of rapamycin may be responsible for its exceptional efficacy.

Accordingly, rapamycin delivered from a local device platform, reduces neointimal hyperplasia by a combination of anti-inflammatory and smooth muscle anti-proliferative effects. Rapamycin used in this context means rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin. Local device platforms include stent coatings, stent sheaths, grafts and local drug infusion catheters or porous balloons or any other suitable means for the in situ or local delivery of drugs, agents or compounds.

The anti-inflammatory effect of rapamycin is evident in data from an experiment, illustrated in Table 6, in which rapamycin delivered from a stent was compared with dexamethasone delivered from a stent. Dexamethasone, a potent steroidal anti-inflammatory agent, was used as a reference standard. Although dexamethasone is able to reduce inflammation scores, rapamycin is far more effective than dexamethasone in reducing inflammation scores. In addition, rapamycin significantly reduces neointimal hyperplasia, unlike dexamethasone.

TABLE 6.0

| Group Rapamycin Rap | N= | Neointimal Area ($mm^2$) | % Area Stenosis | Inflammation Score |
|---|---|---|---|---|
| Uncoated | 8 | 5.24 ± 1.65 | 54 ± 19 | 0.97 ± 1.00 |
| Dexamethasone (Dex) | 8 | 4.31 ± 3.02 | 45 ± 31 | 0.39 ± 0.24 |
| Rapamycin (Rap) | 7 | 2.47 ± 0.94* | 26 ± 10* | 0.13 ± 0.19* |
| Rap + Dex | 6 | 2.42 ± 1.58* | 26 ± 18* | 0.17 ± 0.30* |

*= significance level $P < 0.05$

Rapamycin has also been found to reduce cytokine levels in vascular tissue when delivered from a stent. The data in FIG. 1 illustrates that rapamycin is highly effective in reducing monocyte chemotactic protein (MCP-1) levels in

the vascular wall. MCP-1 is an example of a proinflammatory/chemotactic cytokine that is elaborated during vessel injury. Reduction in MCP-1 illustrates the beneficial effect of rapamycin in reducing the expression of proinflammatory mediators and contributing to the anti-inflammatory effect of rapamycin delivered locally from a stent. It is recognized that vascular inflammation in response to injury is a major contributor to the development of neointimal hyperplasia.

Since rapamycin may be shown to inhibit local inflammatory events in the vessel it is believed that this could explain the unexpected superiority of rapamycin in inhibiting neointima.

As set forth above, rapamycin functions on a number of levels to produce such desired effects as the prevention of T-cell proliferation, the inhibition of negative remodeling, the reduction of inflammation, and the prevention of smooth muscle cell proliferation. While the exact mechanisms of these functions are not completely known, the mechanisms that have been identified may be expanded upon.

Studies with rapamycin suggest that the prevention of smooth muscle cell proliferation by blockade of the cell cycle is a valid strategy for reducing neointimal hyperplasia. Dramatic and sustained reductions in late lumen loss and neointimal plaque volume have been observed in patients receiving rapamycin delivered locally from a stent. The present invention expands upon the mechanism of rapamycin to include additional approaches to inhibit the cell cycle and reduce neointimal hyperplasia without producing toxicity.

The cell cycle is a tightly controlled biochemical cascade of events that regulate the process of cell replication. When cells are stimulated by appropriate growth factors, they move from $G_0$ (quiescence) to the G1 phase of the cell cycle. Selective inhibition of the cell cycle in the G1 phase, prior to DNA replication (S phase), may offer therapeutic advantages of cell preservation and viability while retaining anti-proliferative efficacy when compared to therapeutics that act later in the cell cycle i.e. at S, G2 or M phase.

Accordingly, the prevention of intimal hyperplasia in blood vessels and other conduit vessels in the body may be achieved using cell cycle inhibitors that act selectively at the G1 phase of the cell cycle. These inhibitors of the G1 phase of the cell cycle may be small molecules, peptides, proteins, oligonucleotides or DNA sequences. More specifically, these drugs or agents include inhibitors of cyclin dependent kinases (cdk's) involved with the progression of the cell cycle through the G1 phase, in particular cdk2 and cdk4.

Examples of drugs, agents or compounds that act selectively at the G1 phase of the cell cycle include small molecules such as flavopiridol and its structural analogs that have been found to inhibit cell cycle in the late G1 phase by antagonism of cyclin dependent kinases. Therapeutic agents that elevate an endogenous kinase inhibitory protein$^{kip}$ called P27, sometimes referred to as P27$^{kip1}$, that selectively inhibits cyclin dependent kinases may be utilized. This includes small molecules, peptides and proteins that either block the degradation of P27 or enhance the cellular production of P27, including gene vectors that can transfact the gene to produce P27. Staurosporin and related small molecules that block the cell cycle by inhibiting protein kinases may be utilized. Protein kinase inhibitors, including the class of tyrphostins that selectively inhibit protein kinases to antagonize signal transduction in smooth muscle in response to a broad range of growth factors such as PDGF and FGF may also be utilized.

Any of the drugs, agents or compounds discussed above may be administered either systemically, for example, orally, intravenously, intramuscularly, subcutaneously, nasally or intradermally, or locally, for example, stent coating, stent covering or local delivery catheter. In addition, the drugs or agents discussed above may be formulated for fast-release or slow release with the objective of maintaining the drugs or agents in contact with target tissues for a period ranging from three days to eight weeks.

As set forth above, the complex of rapamycin and FKPB12 binds to and inhibits a phosphoinositide (PI)-3 kinase called the mammalian Target of Rapamycin or TOR. An antagonist of the catalytic activity of TOR, functioning as either an active site inhibitor or as an allosteric modulator, i.e. an indirect inhibitor that allosterically modulates, would mimic the actions of rapamycin but bypass the requirement for FKBP12. The potential advantages of a direct inhibitor of TOR include better tissue penetration and better physical/chemical stability. In addition, other potential advantages include greater selectivity and specificity of action due to the specificity of an antagonist for one of multiple isoforms of TOR that may exist in different tissues, and a potentially different spectrum of downstream effects leading to greater drug efficacy and/or safety.

The inhibitor may be a small organic molecule (approximate mw<1000), which is either a synthetic or naturally derived product. Wortmanin may be an agent which inhibits the function of this class of proteins. It may also be a peptide or an oligonucleotide sequence. The inhibitor may be administered either sytemically (orally, intravenously, intramuscularly, subcutaneously, nasally, or intradermally) or locally (stent coating, stent covering, local drug delivery catheter). For example, the inhibitor may be released into the vascular wall of a human from a nonerodible polymeric stent coating. In addition, the inhibitor may be formulated for fast-release or slow release with the objective of maintaining the rapamycin or other drug, agent or compound in contact with target tissues for a period ranging from three days to eight weeks.

As stated previously, the implantation of a coronary stent in conjunction with balloon angioplasty is highly effective in treating acute vessel closure and may reduce the risk of restenosis. Intravascular ultrasound studies (Mintz et al., 1996) suggest that coronary stenting effectively prevents vessel constriction and that most of the late luminal loss after stent implantation is due to plaque growth, probably related to neointimal hyperplasia. The late luminal loss after coronary stenting is almost two times higher than that observed after conventional balloon angioplasty. Thus, inasmuch as stents prevent at least a portion of the restenosis process, the use of drugs, agents or compounds which prevent inflammation and proliferation, or prevent proliferation by multiple mechanisms, combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

The local delivery of drugs, agents or compounds from a stent has the following advantages; namely, the prevention of vessel recoil and remodeling through the scaffolding action of the stent and the drugs, agents or compounds and the prevention of multiple components of neointimal hyperplasia. This local administration of drugs, agents or compounds to stented coronary arteries may also have additional therapeutic benefit. For example, higher tissue concentrations would be achievable than that which would occur with systemic administration, reduced systemic toxicity, and single treatment and ease of administration. An additional benefit of drug therapy may be to reduce the dose of the therapeutic compounds, thereby limiting their toxicity, while still achieving a reduction in restenosis.

There are a multiplicity of different stents that may be utilized following percutaneous transluminal coronary angioplasty. Although any number of stents may be utilized in accordance with the present invention, for simplicity, one particular stent will be described in exemplary embodiments of the present invention. The skilled artisan will recognize that any number of stents may be utilized in connection with the present invention.

A stent is commonly used as a tubular structure left inside the lumen of a duct to relieve an obstruction. Commonly, stents are inserted into the lumen in a non-expanded form and are then expanded autonomously, or with the aid of a second device in situ. A typical method of expansion occurs through the use of a catheter-mounted angioplasty balloon which is inflated within the stenosed vessel or body passageway in order to shear and disrupt the obstructions associated with the wall components of the vessel and to obtain an enlarged lumen. As set forth below, self-expanding stents may also be utilized.

FIG. **2** illustrates an exemplary stent **100** which may be utilized in accordance with an exemplary embodiment of the present invention. The expandable cylindrical stent **100** comprises a fenestrated structure for placement in a blood vessel, duct or lumen to hold the vessel, duct or lumen open, more particularly for protecting a segment of artery from restenosis after angioplasty. The stent **100** may be expanded circumferentially and maintained in an expanded configuration, that is circumferentially or radially rigid. The stent **100** is axially flexible and when flexed at a band, the stent **100** avoids any externally-protruding component parts.

The stent **100** generally comprises first and second ends with an intermediate section therebetween. The stent **100** has a longitudinal axis and comprises a plurality of longitudinally disposed bands **102**, wherein each band **102** defines a generally continuous wave along a line segment parallel to the longitudinal axis. A plurality of circumferentially arranged links **104** maintain the bands **102** in a substantially tubular structure. Essentially, each longitudinally disposed band **102** is connected at a plurality of periodic locations, by a short circumferentially arranged link **104** to an adjacent band **102**. The wave associated with each of the bands **102** has approximately the same fundamental spatial frequency in the intermediate section, and the bands **102** are so disposed that the wave associated with them are generally aligned so as to be generally in phase with one another. As illustrated in the figure, each longitudinally arranged band **102** undulates through approximately two cycles before there is a link to an adjacent band.

The stent **100** may be fabricated utilizing any number of methods. For example, the stent **100** may be fabricated from a hollow or formed stainless steel tube that may be machined using lasers, electric discharge milling, chemical etching or other means. The stent **100** is inserted into the body and placed at the desired site in an unexpanded form. In one embodiment, expansion may be effected in a blood vessel by a balloon catheter, where the final diameter of the stent **100** is a function of the diameter of the balloon catheter used.

It should be appreciated that a stent **100** in accordance with the present invention may be embodied in a shape-memory material, including, for example, an appropriate alloy of nickel and titanium. In this embodiment, after the stent **100** has been formed it may be compressed so as to occupy a space sufficiently small as to permit its insertion in a blood vessel or other tissue by insertion means, wherein the insertion means include a suitable catheter, or flexible rod. On emerging from the catheter, the stent **100** may be configured to expand into the desired configuration where the expansion is automatic or triggered by a change in pressure, temperature or electrical stimulation.

FIG. **3** illustrates an exemplary embodiment of the present invention utilizing the stent **100** illustrated in FIG. **2**. As illustrated, the stent **100** may be modified to comprise a reservoir **106**. Each of the reservoirs may be opened or closed as desired. These reservoirs **106** may be specifically designed to hold the drug, agent, compound or combinations thereof to be delivered. Regardless of the design of the stent **100**, it is preferable to have the drug, agent, compound or combinations thereof dosage applied with enough specificity and a sufficient concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the bands **102** is preferably sized to adequately apply the drug/drug combination dosage at the desired location and in the desired amount.

In an alternate exemplary embodiment, the entire inner and outer surface of the stent **100** may be coated with various drug and drug combinations in therapeutic dosage amounts. A detailed description of exemplary coating techniques is described below.

Rapamycin or any of the drugs, agents or compounds described above may be incorporated into or affixed to the stent in a number of ways and utilizing any number of biocompatible materials. In the exemplary embodiment, the rapamycin is directly incorporated into a polymeric matrix and sprayed onto the outer surface of the stent. The rapamycin elutes from the polymeric matrix over time and enters the surrounding tissue. The rapamycin preferably remains on the stent for at least three days up to approximately six months and more preferably between seven and thirty days.

Any number of non-erodible polymers may be utilized in conjunction with rapamycin. In the exemplary embodiment, the polymeric matrix comprises two layers. The base layer comprises a solution of ethylene-co-vinylacetate and polybutylmethacrylate. The rapamycin is incorporated into this layer. The outer layer comprises only polybutylmethacrylate and acts as a diffusion barrier to prevent the rapamycin from eluting too quickly and entering the surrounding tissues. The thickness of the outer layer or top coat determines the rate at which the rapamycin elutes from the matrix. Essentially, the rapamycin elutes from the matrix by diffusion through the polymer molecules. Polymers tend to move, thereby allowing solids, liquids and gases to escape therefrom. The total thickness of the polymeric matrix is in the range from about 1 micron to about 20 microns or greater. In a preferred exemplary embodiment, the base layer, including the polymer and drug, has a thickness in the range from about 8 microns to about 12 microns and the outer layer has a thickness in the range from about 1 micron to about 2 microns.

The ethylene-co-vinylacetate, polybutylmethacrylate and rapamycin solution may be incorporated into or onto the stent in a number of ways. For example, the solution may be sprayed onto the stent or the stent may be dipped into the solution. In a preferred embodiment, the solution is sprayed onto the stent and then allowed to dry. In another exemplary embodiment, the solution may be electrically charged to one polarity and the stent electrically changed to the opposite polarity. In this manner, the solution and stent will be attracted to one another. In using this type of spraying process, waste may be reduced and more control over the thickness of the coat may be achieved.

Since rapamycin works by entering the surrounding tissue, it is preferably only affixed to the surface of the stent making contact with one tissue. Typically, only the outer surface of the stent makes contact with the tissue. Accord-

ingly, in a preferred embodiment, only the outer surface of the stent is coated with rapamycin. For other drugs, agents or compounds, the entire stent may be coated.

It is important to note that different polymers may be utilized for different stents. For example, in the above-described embodiment, ethylene-co-vinylacetate and polybutylmethacrylate are utilized to form the polymeric matrix. This matrix works well with stainless steel stents. Other polymers may be utilized more effectively with stents formed from other materials, including materials that exhibit superelastic properties such as alloys of nickel and titanium.

Although shown and described is what is believed to be the most practical and preferred embodiments, it is apparent that departures from specific designs and methods described and shown will suggest themselves to those skilled in the art and may be used without departing from the spirit and scope of the invention. The present invention is not restricted to the particular constructions described and illustrated, but should be constructed to cohere with all modifications that may fall within the scope of the appended claims.

What is claimed is:

**1**. A drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and from about 64 μg to about 197 μg of rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said device provides an in-stent late loss in diameter at 12 months following implantation in a human of less than about 0.5 mm, as measured by quantitative coronary angiography.

**2**. A drug delivery device according to claim **1** that provides an in- stent late loss in diameter at 12 months following implantation in a human of less than about 0.3 mm, as measured by quantitative coronary angiography.

**3**. A drug delivery device according to claim **1** or **2** that provides an in-stent diameter stenosis at 12 months following implantation in a human of less than about 22%, as measured by quantitative coronary angiography.

**4**. A drug delivery device according to claim **3** that provides an in-stent diameter stenosis at 12 months following implantation in a human of less than about 15%, as measured by quantitative coronary angiography.

**5**. A drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and from about 64 μg to about 197 μg of rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said device provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.5 mm, as measured by quantitative coronary angiography.

**6**. A drug delivery device according to claim **5** that provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.3 mm, as measured by quantitative coronary angiography.

**7**. A drug delivery device according to claim **5** or **6** that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 22%, as measured by quantitative coronary angiography.

**8**. A drug delivery device according to claim **7** that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 15%, as measured by quantitative coronary angiography.

**9**. A method of inhibiting neointimal proliferation in a human coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting in the lumen of said coronary artery a drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and from about 64 μg to about 197 μg of rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said method provides an in-stent late loss in diameter at 12 months following implantation of less than about 0.5 mm, as measured by quantitative coronary angiography.

**10**. A method according to claim **9** that provides an in-stent late loss in diameter at 12 months following implantation of less than about 0.3 mm, as measured by quantitative coronary angiography.

**11**. A method according to claim **9** or **10** that provides an in-stent diameter stenosis at 12 months following implantation of less than about 22%, as measured by quantitative coronary angiography.

**12**. A method according to claim **11** that provides an in-stent diameter stenosis at 12 months following implantation of less than about 15%, as measured by quantitative coronary angiography.

**13**. A method of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting in the lumen of said coronary artery a drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and from about 64 μg to about 197 μg of rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said method provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.5 mm, as measured by quantitative coronary angiography.

**14**. A method according to claim **13** that provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.3 mm, as measured by quantitative coronary angiography.

**15**. A method according to claim **13** or **14** that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 22%, as measured by quantitative coronary angiography.

**16**. A method according to claim **15** that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 15%, as measured by quantitative coronary angiography.

**17**. The drug delivery device according to any one of claims **1**, **2**, **4** or **5** wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 64 μg to about 125 μg.

**18**. The drug delivery device according to to any one of claims **1**, **2**, **4** or **5** that releases a portion of said dose of rapamycin or a macrocyclic triene analog thereof at about six weeks following intraluminal implantation.

**19**. The drug delivery device according to any one of claims **1**, **2**, **4** or **5** wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 2 μg to about 30 μg per millimeter of stent length.

**20**. The drug delivery device according to claim **19** wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 3 μg to about 13 μg per millimeter of stent length.

21. The drug delivery device according to claim **19** that releases a portion of said dose of rapamycin or a macrocyclic triene analog thereof at about six weeks following intraluminal implantation.

22. The method according to any one of claims **9**, **10**, **13** or **14**, wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 64 μg to about 125 μg.

23. The method according to any one of claims **9**, **10**, **13** or **14**, wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 2 μg to about 30 μg per millimeter of stent length.



24. The method according to any one of claims **9**, **10**, **13** or **14**, wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 3 μg to about 13 μg per millimeter of stent length.

25. The method according to any one of claims **9**, **10**, **13** or **14**, wherein said drug delivery device releases a portion of said dose of rapamycin or a macrocyclic triene analog thereof at about six weeks following intraluminal implantation.

* * * * *

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(12) **United States Patent**
**Rosenthal et al.**

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(54) **MEDICAL DEVICE FOR DELIVERING BIOLOGICALLY ACTIVE MATERIAL**

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*A61F 2/06* (2006.01)

(52) **U.S. Cl.** ..... **623/1.42**

(58) **Field of Classification Search** ..... 623/1.11–1.48
See application file for complete search history.

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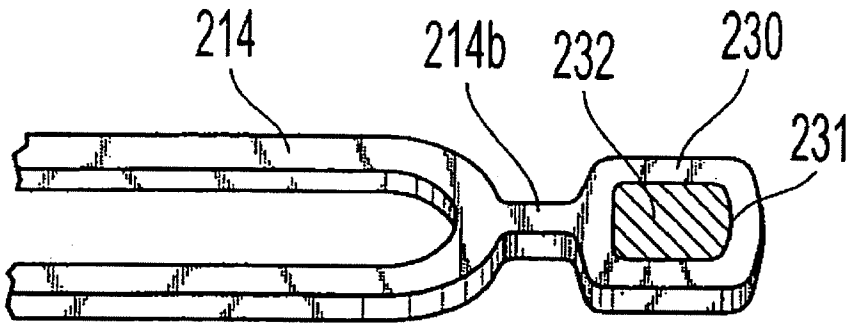
(57) **ABSTRACT**

This invention relates generally to a stent comprising a plurality of struts and a plurality of projecting elements integral with the struts. At least some of the struts and some of the projecting elements comprise a biologically active material. The struts are configured in a tubular shape or tubular sidewall having two ends. One end of at least one of the projecting elements defines an end of the stent when the stent is expanded. The invention is also directed to a method for delivering the biologically active material to body tissue of a patient by inserting such an expandable stent into body of the patient. The invention is further directed to a system comprising the expandable stent and a balloon catheter for expanding the stent.

**28 Claims, 13 Drawing Sheets**



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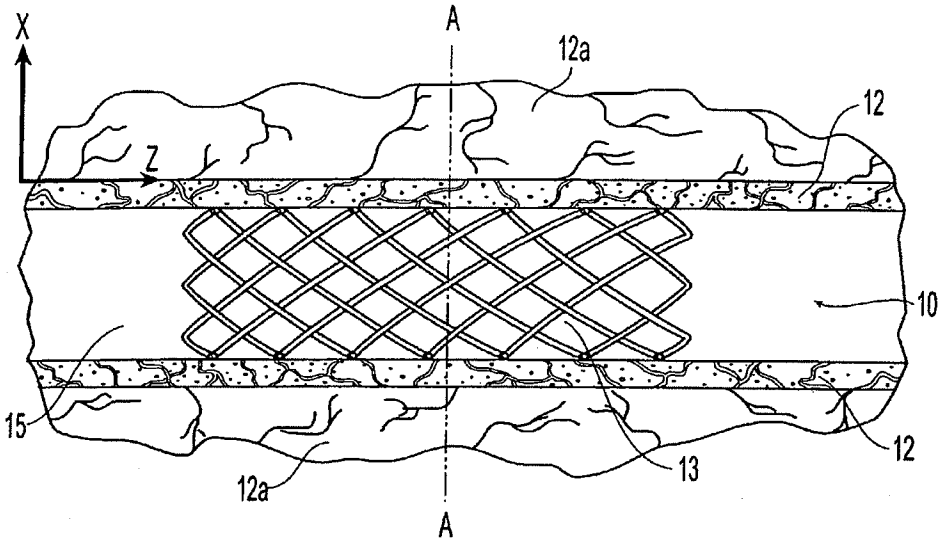



*Fig. 1*

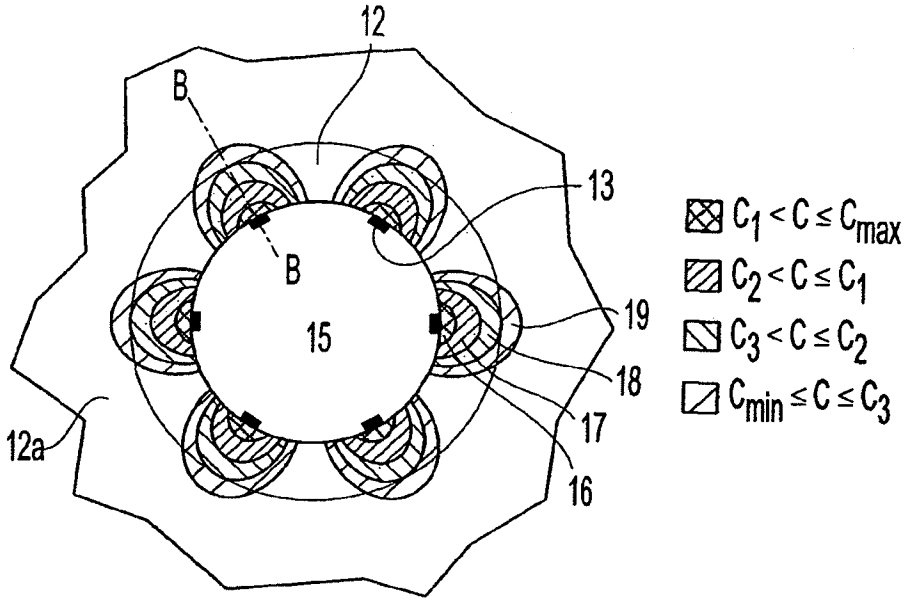

12
B
B
13
15
19
18
17
16
12a
$C_1 < C \leq C_{max}$
$C_2 < C \leq C_1$
$C_3 < C \leq C_2$
$C_{min} \leq C \leq C_3$

*Fig. 2A*

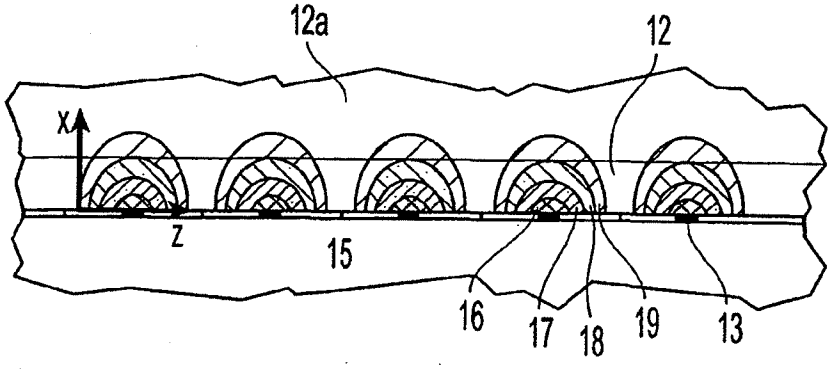

12a
12
x
z
15
16
17
18
19
13

*Fig. 2B*

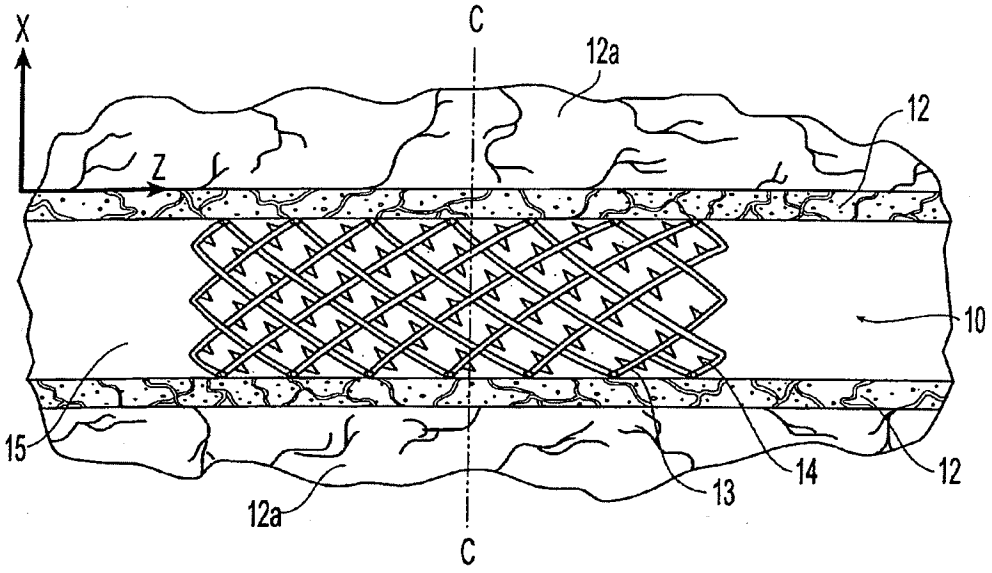



*Fig. 3*

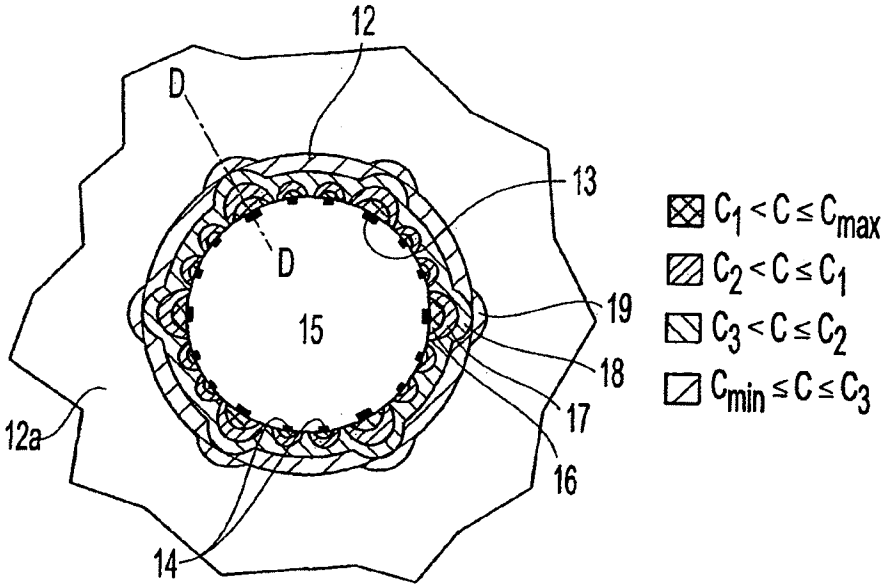

12
D
13
D
15
19
18
17
16
12a
14
$C_1 < C \leq C_{max}$
$C_2 < C \leq C_1$
$C_3 < C \leq C_2$
$C_{min} \leq C \leq C_3$

*Fig. 4A*

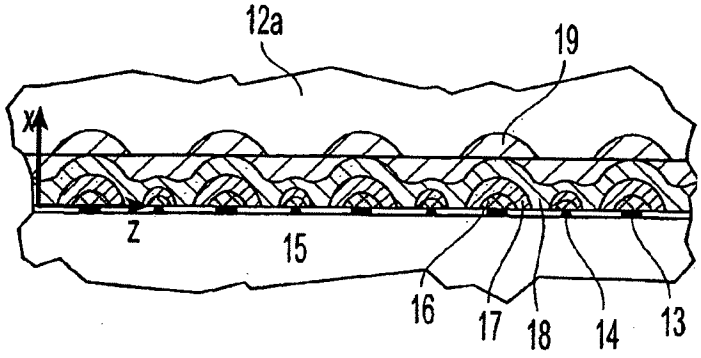

12a
19
x
z
15
16
17
18
14
13

*Fig. 4B*

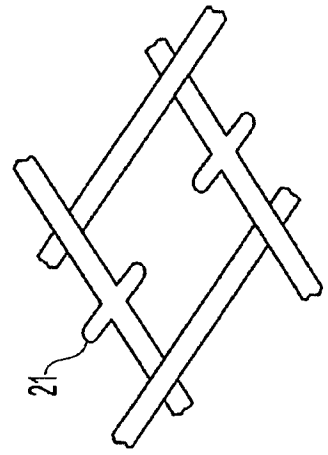



Fig. 6

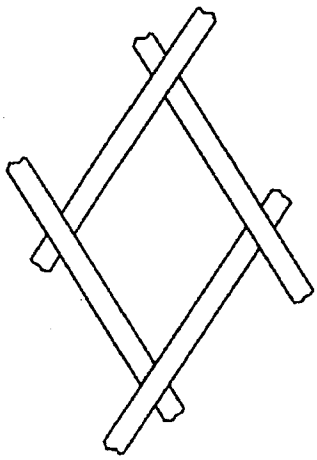


Fig. 5

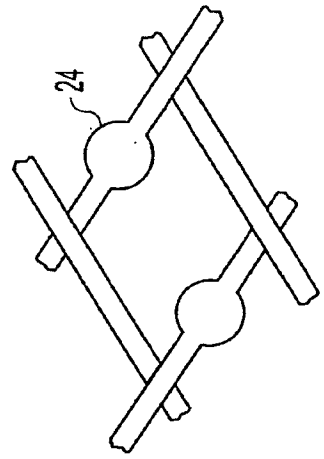



Fig. 9

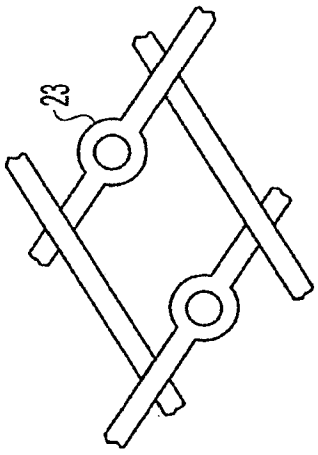



Fig. 8

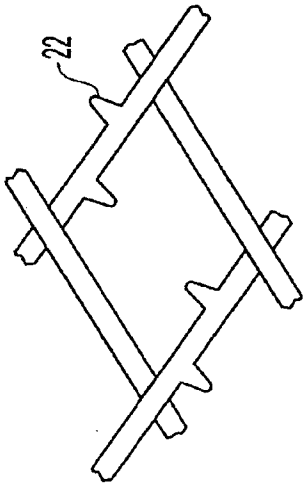



Fig. 7

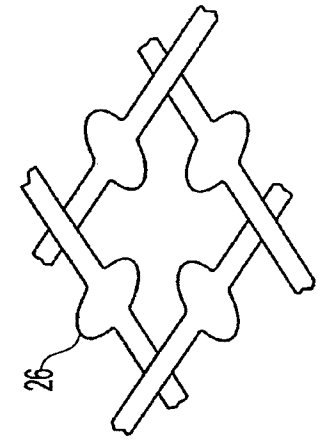



Fig. 11

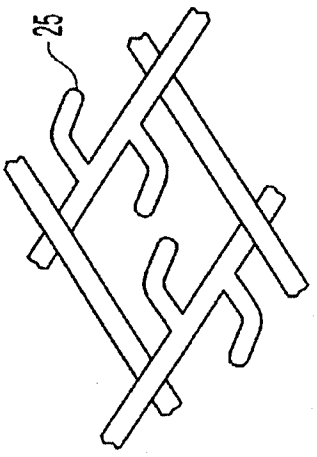



Fig. 10

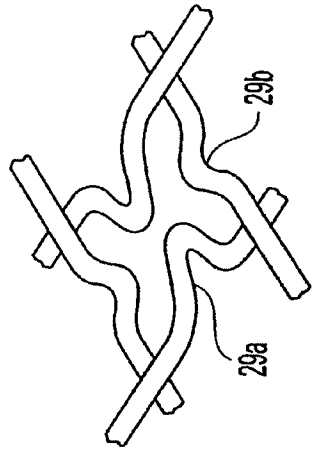



Fig. 14

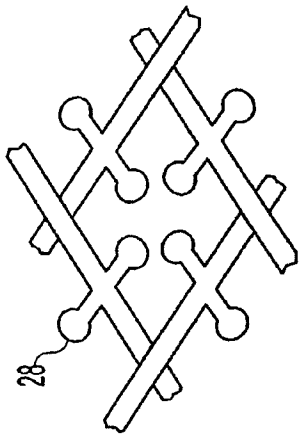



Fig. 13

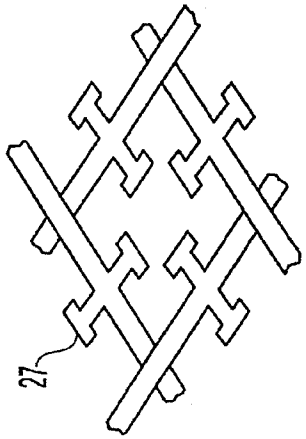



Fig. 12

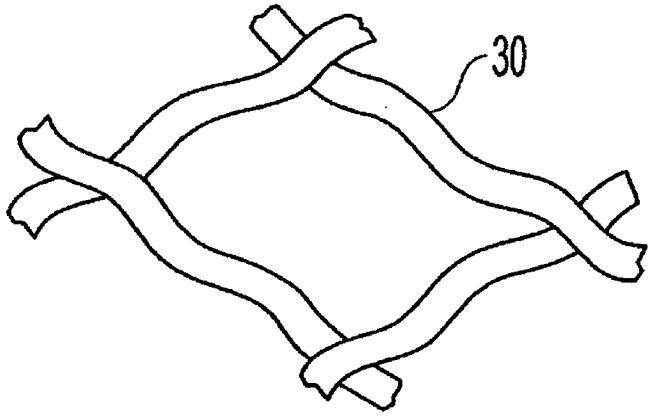
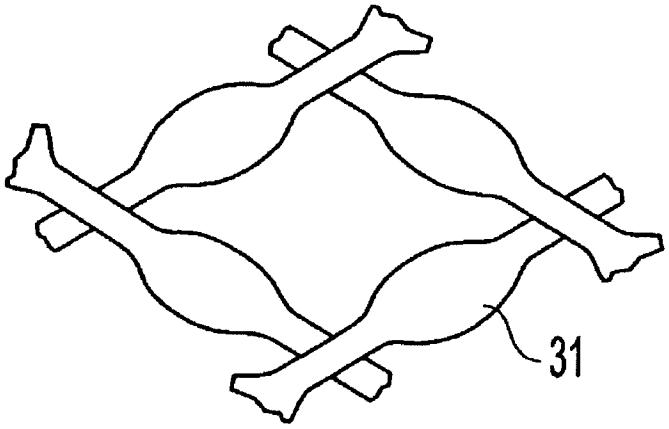



*Fig. 15*




*i . 16*

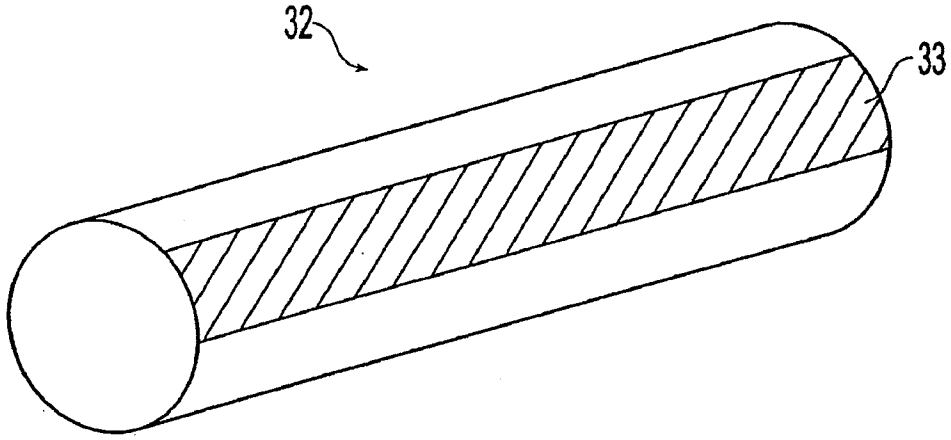



*Fig. 17*

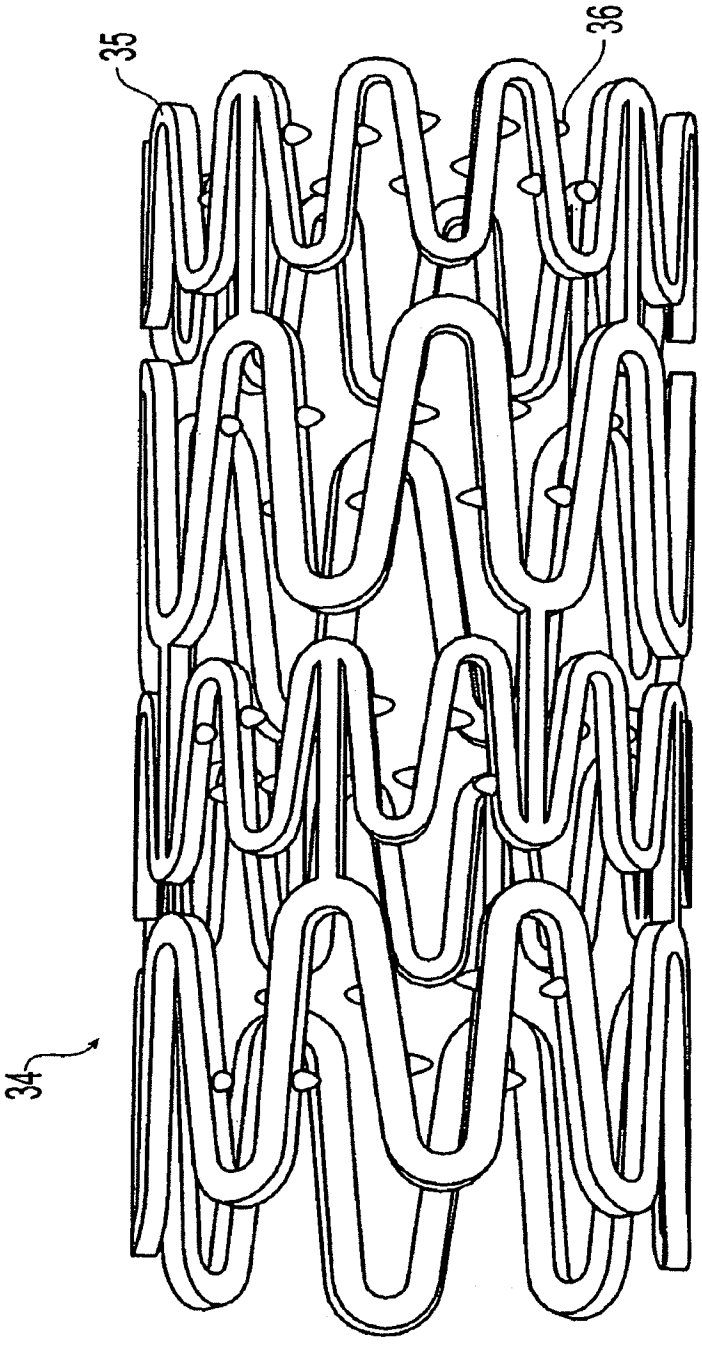



*Fig. 18*

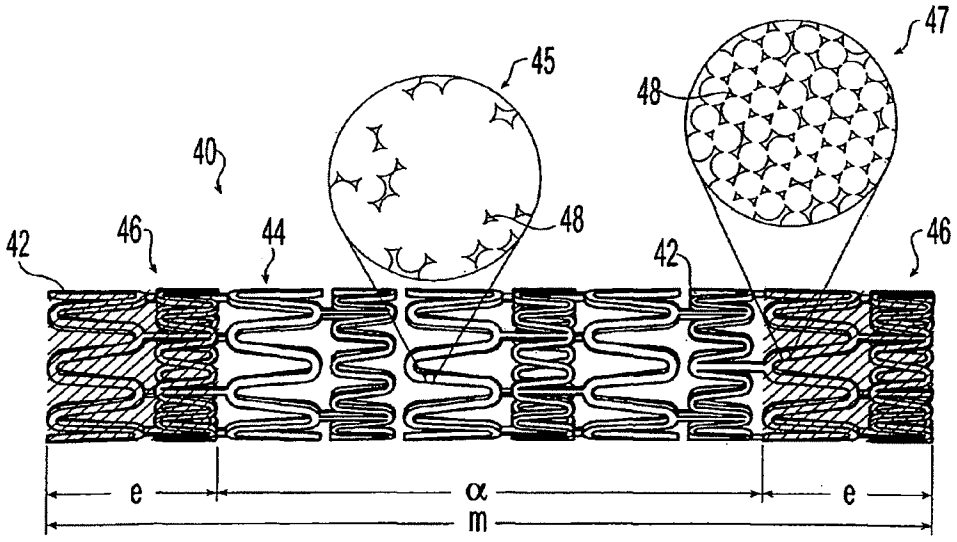



*Fig. 19*

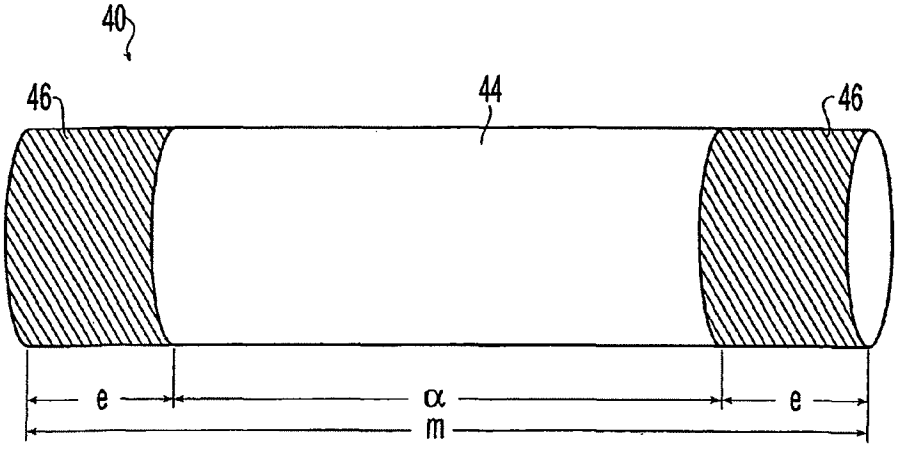
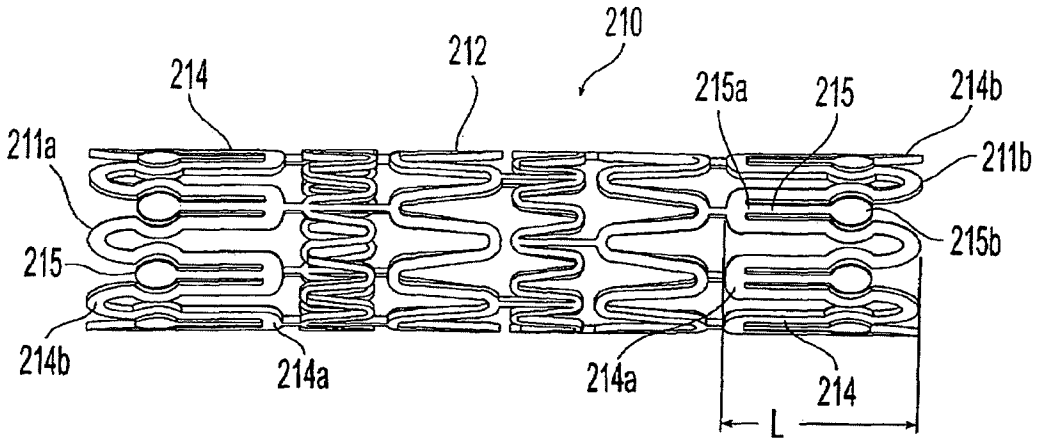



*Fig. 20*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215a
215
214b
211a
211b
215b
215
214b
214a
214a
214
L

*Fig. 21*

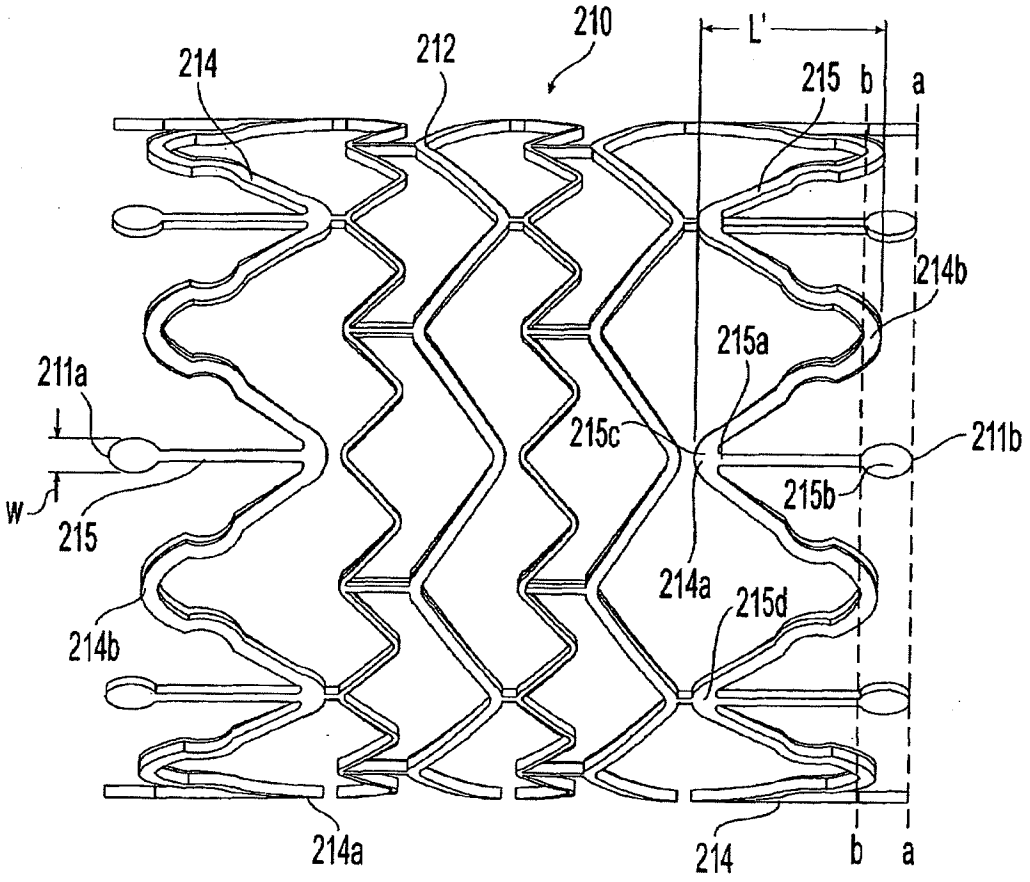

210
L'
214
212
215
b
a
214b
215a
211a
215c
211b
w
215b
215
214a
215d
214b
214a
214
b
a

*Fig. 22*

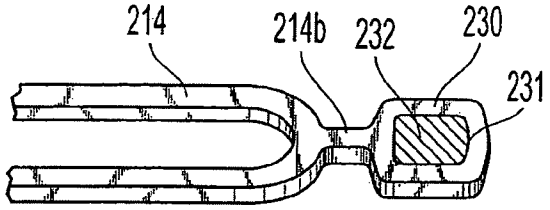



*Fig. 23*

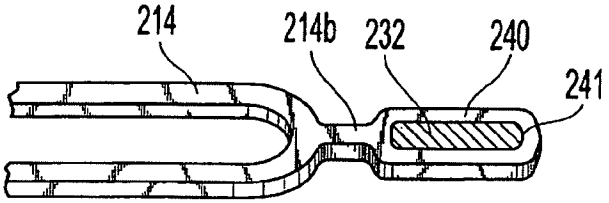



*Fig. 24*

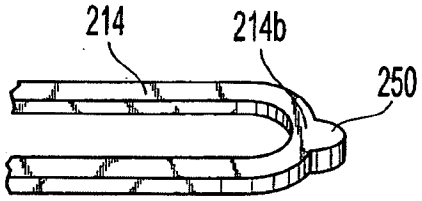



*Fig. 25*

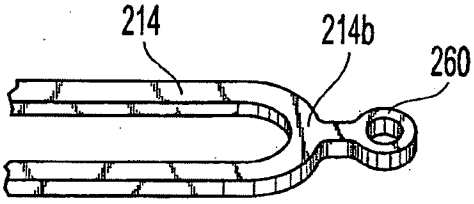



*Fig. 26*

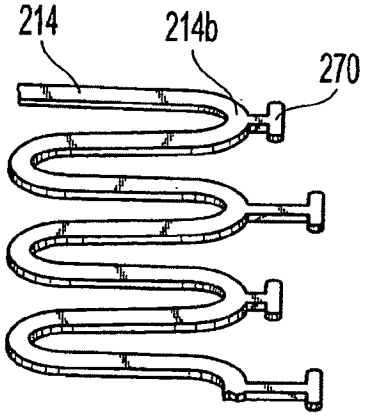



*Fig. 27*

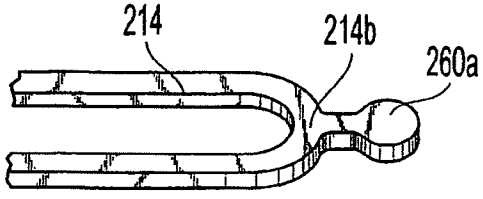



*Fig. 26A*

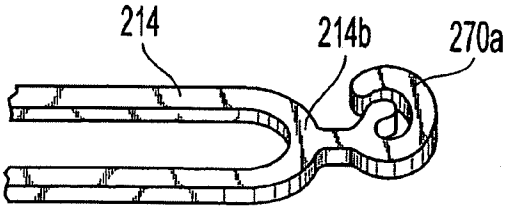



*Fig. 27A*

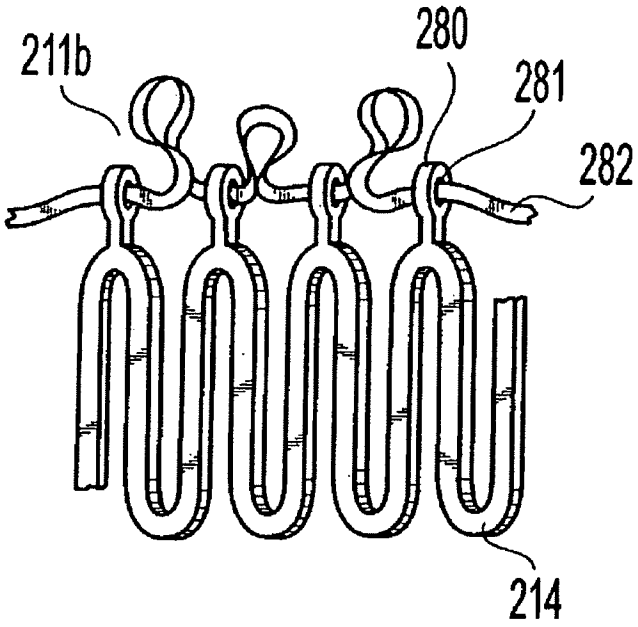
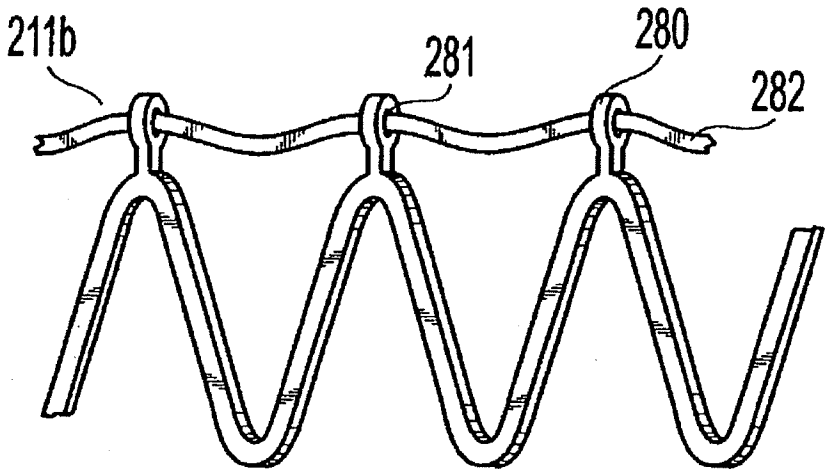



*Fig. 28*




*i . 29*

# MEDICAL DEVICE FOR DELIVERING BIOLOGICALLY ACTIVE MATERIAL

## FIELD OF THE INVENTION

This is a continuation-in-part of co-pending U.S. patent application Ser. No. 10/062,794, filed Jan. 31, 2002, which is incorporated herein by reference.

This invention relates generally to medical devices, such as stents, for delivering a biologically active material to a desired location within the body of a patient. More particularly, the invention is directed to a medical device comprising a plurality of struts and a plurality of non-structural elements integral with the struts, wherein the struts and the non-structural elements comprise the biologically active material. The invention is also directed to a method for delivering the biologically active material to the body tissue of a patient by inserting this medical device into the body of the patient, and further a method for designing such medical device.

The invention is also directed to a medical device comprising a plurality of struts and having an outer surface which has a middle section and end sections. The end sections of the outer surface either (1) contain a greater amount of a biologically active material per unit length of the outer surface or (2) have a greater capacity per unit length to contain such material than the middle section of the outer surface by having a greater surface area per unit length of the outer surface than the middle section or having a greater affinity for the biologically active material per unit length of the outer surface than the middle section.

Furthermore, this invention relates generally to a stent comprising a plurality of struts and a plurality of projecting elements integral with the struts. At least some of the struts and some of the projecting elements comprise a biologically active material. The struts are configured in a tubular shape or tubular sidewall having two ends. One end of at least one of the projecting elements defines the end of the stent when the stent is expanded. The invention is also directed to a method for delivering the biologically active material to the body tissue of a patient by inserting such an expandable stent into the body of the patient. The invention is further directed to a system comprising the expandable stent and a balloon catheter for expanding the stent.

## BACKGROUND OF THE INVENTION

Balloon angioplasty has been very effective in treating stenosis, i.e., to open blocked vessels and restore normal levels of blood flow. However, although once a blocked vessel is opened, the treated vessel can restenose, i.e., reclose, shortly after the procedure. Thus, patients may have to undergo repeated angioplasty or even surgery.

Implantable stent prosthesis or stents are used to reduce restenosis after balloon angioplasty or other procedures using catheters. A stent in the form of a wire mesh tube props open an artery that has recently been cleared using angioplasty. A balloon expendable stent is collapsed to a small diameter, placed over an angioplasty balloon catheter and moved into the area of the blockage. When the balloon is inflated, the stent expands, locks in place and forms a scaffold to hold the artery open. A self-expandable stent is collapsed to a small diameter by placing in a sheath, and expands in the area of the blockage when the sheath surrounding the stent is removed. Usually, the stent stays in the artery permanently, holds it open, improves blood flow to the heart muscle and relieves symptoms. The stent procedure is fairly common, and various types of stents have been developed and actually used.



A variety of medical conditions have been treated by introducing an insertable medical device having a coating for release of a biologically active material. For example, various types of biologically active material-coated medical devices, such as stents, have been proposed for localized delivery of the biologically active material to a body lumen, such as to reduce the possibility of restenosis. See, e.g., U.S. Pat. No. 6,099,562 to Ding et al. However, it has been noted that, with existing coated medical devices, the release profile of a biologically active material may not be uniform along the entire length of the medical device.

For example, even if a biologically active material having a pharmacological effect is delivered to a body tissue, such effect may not result if the concentration of the biologically active material in the body tissue is below a certain concentration. Such concentration is referred to as the minimum effective concentration ($C_{min}$) of the biologically active material in the body tissue. Each biologically active material has different $C_{min}$. $C_{min}$ of a biologically active material also varies depending on the type of body tissue to which it is delivered. On the other hand, a biologically active material becomes toxic if its concentration is higher than a certain concentration. Such concentration is referred to as the maximum effective concentration $C_{max}$. In addition, it is insufficient that the mean concentration of the biologically active material delivered through out the body tissue to be treated is greater than $C_{min}$ and smaller than $C_{max}$. The concentration of the biologically active material at each and every area throughout the body tissue to be treated should be equal to or greater than $C_{min}$ but equal to or smaller than $C_{max}$ of the biologically active material. For instance, when a coated stent comprised of struts, such as the stent shown in FIG. **1**, is used as a medical device for delivering a hydrophobic biologically active material, concentrations of the biologically active material may significantly differ between the regions of the tissue adjacent to the struts and the regions of the tissue farther from the struts. See Hwang et al., http://www.circulationaha.org (accepted in April 2001). Even if the mean concentration of the biologically active material in the tissue surrounding the stent is above $C_{min}$ of the biologically active material and at or under $C_{max}$, the concentrations at certain regions of the tissue to be treated, which are farther from the struts, may not reach $C_{min}$. Also, if the amount of the biologically active material in the coating is increased to achieve a concentration higher than $C_{min}$ at all regions of the tissue to be treated, then the concentrations at regions of the tissue adjacent to the struts may exceed the toxic levels, as explained below using the figures.

In FIG. **1**, the coated stent **10** is placed in a blood vessel **15** having a vessel wall **12** to be treated. This vessel wall is surrounded by tissue **12***a*. The biologically active material coated on struts **13** of the stent **10** is released into the vessel wall **12** to be treated. FIG. **2** is a cross sectional view along line A of the stent **10** in FIG. **1**. FIG. **2** also shows the concentration levels of the biologically active material in each area surrounding the struts **13** at a certain time after the insertion of the stent into the vessel **15**. The area adjacent to the struts, i.e., the area between the struts **13** and line **16**, has a concentration level at or below $C_{max}$, which is just below the toxic level. The farther from the struts **13** the tissue to be treated is located, the lower the concentration of the biologically active material delivered to the tissue becomes. However, the area between line **18** and line **19** has the

concentration level at or higher than $C_{min}$. A concentration of the biologically active material in the area outside line **19** is below $C_{min}$.

Also, FIGS. **2**A and **2**B clearly show that there are gaps between each strut **13** wherein the vessel wall to be treated does not receive sufficient biologically active material to have $C_{min}$. The areas within line **19**, i.e., having concentrations above $C_{min}$, may be increased in size to include more area of the vessel wall **12** to be treated, if the amount of the biologically active material on the struts **13** is increased. However, by doing so, the concentration of the biologically active material in the area adjacent to the struts **13** may exceed the toxic level. Accordingly, there is a need for a medical device comprising a plurality of struts that can achieve the biologically active material concentration that is above $C_{min}$ and below toxic levels throughout the tissue.

Also, generally with existing coated medical devices, the coating is uniformly applied along the entire length of the device or surface of the device. For example, conventional coated stents are coated uniformly along the entire length of the surface of the device. The biologically active material-concentration-profile along the length of the coated surface may be in the shape of a bell-curve, wherein the concentration of the biologically active material released at the middle of the surface is greater than the concentration of the biologically active material released at the ends of the coated surface. This uneven concentration-profile along the length of the coated surface may lead to the application of an inadequate or sub-optimal dosage of the biologically active material to the body tissue located at the ends of the coated surface. It is possible that such uneven local concentration of the biologically active material along the length of the coated surface of the medical device may lead to undesired effects. For example, in the case of a biologically active material-coated stent used to prevent or treat restenosis, if the amount of biologically active material delivered to the tissue located at the ends of the stent is sub-optimal, it is possible that restenosis may occur in such tissue. In fact, recent data show that restenosis occurs at the edges of the stents about five times more often than at the middle portion of stents, i.e., the "edge effect". The "edge effect" may be caused by the lesser concentration of biological active material that is present in body tissue in proximity to the edges of the stent.

The biologically active material dosage at the tissue located at the ends of the coated surface of the medical device can be increased if the concentration or amount of the biologically active material is increased along the entire length of the surface. However, by increasing the concentration or amount of biologically active material released along the entire surface, the dosage delivered to tissue located at the middle of the surface may be too great or even at toxic levels. Thus, there is a need for a medical device that can realize a more uniform concentration-profile for biologically active material along the entire length of a coated surface of a medical device and avoid the possibility of undesired effects accompanied by an uneven biologically active material concentration-profile.

Moreover, medical devices wherein a biologically active material is uniformly coated on the entire outer surface of the medical devices that is exposed to body tissue are generally used to deliver such biologically active material to specific parts of such body tissue. For instance, such devices are used to treat lesions in body lumen. However, because the entire outer surface of the device contains the biologically active material, this biologically active material will be delivered to healthy body tissue in addition to the lesion. Treatment of healthy tissue with the biologically active material is not only unnecessary but maybe harmful. Accordingly, there is a need for a medical device that can realize an asymmetry release-profile of biologically active material to deliver such material to only a limited region of the body tissue that requires the biologically active material.

Also, the pressure or stress that the stent exerts against the surrounding tissue is concentrated at the edges of the stent. Such concentrated stress may also contribute to the "edge effect". Therefore, to reduce the "edge effect," there is a need for a stent having a structure wherein the stress exerted against the body tissue in proximity to the edges of the stent is reduced and such body tissue is exposed to a greater amount of biologically active material.

Furthermore, when a balloon and a balloon expandable stent disposed on the balloon are expanded, the ends of the stent generally do not extend to the ends of the balloon, i.e., the ends of the stent do not cover the entire balloon's length. Thus, the balloon inflates beyond the margins or ends of the stents, and the portions of the balloon beyond the stents' ends directly contact the patient's lumen wall. Such direct contact with the balloon may cause a tissue injury in the patient's lumen wall. Also, to reduce such potential injury by using a balloon having a length which is matched exactly to a stent length is impractical because: (1) it is difficult to align the stent with the balloon during crimping; (2) both stent and balloon are manufactured within a small but finite tolerance that provides a range of component sizes; and (3) stents will be shortened during expansion. Therefore, there is a need for a stent having structure to reduce such potential injury caused by the ends or edges of the balloon.

## SUMMARY OF THE INVENTION

These and other objectives are accomplished by the present invention. To achieve the aforementioned objectives, we have invented a medical device for delivering a biologically active material into a body tissue of a patient; a method for designing such device; and a method for delivery of a biologically active material to a body tissue.

The medical device of the invention is a medical device for delivery of biologically active materials to a body tissue of a patient in need of treatment. The medical device comprises struts and non-structural elements integral with the struts, and those struts and non-structural elements comprise the biologically active material. In an embodiment, the medical device comprises a tubular portion having an outer surface, and the non-structural elements are distributed throughout the outer surface. In another embodiment, the non-structural elements are located in a radially asymmetric distribution on the outer surface. In yet another embodiment, the outer surface has end sections and a middle section, and the end sections comprise a greater number of the non-structural elements per unit length of the outer surface than the middle section.

The present invention is also directed to a method for delivering a biologically active material to the body tissue of a patient which comprises inserting the above-mentioned medical device into the body of the patient.

Further, the present invention is directed to a method for designing such medical device. The method comprises: providing a preliminary medical device comprising struts in a geometric pattern wherein the struts comprise the biologically active material; determining a concentration-profile for the biologically active material which is released from the preliminary medical device; and modifying the geometric pattern of the struts of the preliminary medical device by

incorporating non-structural elements comprising the biologically active material that are integral with the struts to achieve more desired distribution of the biologically active material in the body tissue.

The present invention is also directed to a medical device insertable into the body of a patient. The medical device has an outer surface comprising struts, and the outer surface has a middle section and end sections. The end sections have a greater available surface area per unit length of the outer surface than the middle section. In another embodiment, the end sections have greater affinity for the biologically active material per unit length of the outer surface than the middle section. In yet another embodiment, the end sections have a greater amount of the biologically active material per unit length of the outer surface than the middle section. Further, in another embodiment, at least a part of each of the middle section and the end sections is covered with a coating comprising the biologically active material, and the middle section comprises a barrier layer placed over the coating covering the middle section.

Moreover, the present invention provides another embodiment of the medical device for treating body tissue. The medical device comprises an outer surface comprising struts. The outer surface has a rectangular portion having a greater capacity for carrying or containing a biologically active material per unit length of the outer surface than the parts of the outer surface that are outside the rectangular portion. In the alternative, the rectangular portion may have a greater affinity for the biologically active material. The present invention is also directed to a method for delivering a biologically active material by inserting the above-mentioned medical device comprising the biologically active material in such a way that the rectangular portion is in direct contact with the body tissue in need of treatment.

Additionally, the present invention is directed to an expandable stent comprising two ends and a tubular sidewall between the two ends. The sidewall comprises a plurality of struts, and a plurality of projecting elements located proximate at least one stent end. Each projecting element comprises a first end and a second end, in which the first projecting element end is integral with or attached to a strut. The second projecting element end is capable of defining at least one stent end when the stent is in an expanded position. Also, at least one of the struts or at least one of the projecting elements comprises a biologically active material.

Moreover, the invention is directed to a balloon expandable stent comprising two ends and a tubular sidewall between the two ends, in which the sidewall comprises a plurality of struts and a plurality of projecting elements proximate at least one stent end. Each projecting element comprises a first end and a second end. The first projecting element end is integral with or attached to a strut; and the second projecting element end is capable of defining at least one stent end when the stent is in an expanded position. At least one of the projecting elements comprise a biologically active material.

In addition, the present invention is directed to a system comprising a balloon expandable stent and a balloon catheter having an inflatable balloon for expanding the stent to an expanded position. The stent comprises two ends and a tubular sidewall between the two ends, and the sidewall comprises a plurality of struts as well as a plurality of projecting elements proximate at least one stent end. Each projecting element comprises a first end and a second end. The first projecting element end is integral with or attached to a strut; and the second projecting element end is capable of defining at least one stent end when the stent is in the expanded position. Also, at least one of the struts or one of the projecting elements comprise a biologically active material.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** depicts a side view of a stent without non-structural elements in a cross-sectioned blood vessel. The stent is coated with a biologically active material.

FIGS. **2**A and **2**B depict cross sectional views of the stent and blood vessel of FIG. **1** along line A-A and line B-B (shown in FIG. **2**A), respectively. FIGS. **2**A and **2**B also show areas of body tissue having different concentration levels of the biologically active material.

FIG. **3** depicts a side view of a stent with non-structural elements in a cross-sectioned blood vessel. The stent is coated with a biologically active material.

FIGS. **4**A and **4**B depict cross sectional views of the stent and blood vessel of FIG. **3** along line C-C and line D-D (shown in FIG. **4**A), respectively. FIGS. **4**A and **4**B also show areas having different concentration levels of the biologically active material.

FIG. **5** depicts struts of a conventional expandable stent.

FIGS. **6-14**, each depicts struts having non-functional elements integral with the struts.

FIG. **15** depicts wavy struts that have greater surface area per unit length of the strut than conventional struts.

FIG. **16** depicts struts having a greater average diameter per length of the strut than the conventional struts.

FIG. **17** depicts a simplified view of a stent having a rectangular portion of the outer surface where non-structural elements are located, and the rectangular portion is shown by hatching.

FIG. **18** depicts a perspective view of a stent wherein non-structural elements are located only in a rectangular portion of the outer surface.

FIG. **19** depicts a stent having end sections and a middle section and comprised of struts, wherein the end sections are comprised of a porous material and the middle section is comprised of a less porous material.

FIG. **20** is a simplified view of a stent which shows the outer surface, having end sections and a middle section.

FIG. **21** depicts a side view of a stent comprised of a plurality of struts and projecting elements in an unexpanded state.

FIG. **22** depicts the stent of FIG. **21** in an expanded state.

FIG. **23** depicts a projecting element in a shape of a rod having a rectangular-end integral to a strut.

FIG. **24** depicts another projecting element in a shape of a rod having a paddle-shaped end integral to a strut.

FIGS. **25***a*-**27***a* depict projecting elements in the shape of rods having various shaped ends integral to a strut.

FIG. **28** depicts a part of an unexpanded stent where the projecting elements are in the shape of a rod with an opening such as a loop at its end.

FIG. **29** shows the stent of FIG. **28** in an expanded state.

## DETAILED DESCRIPTION OF THE INVENTION

1. Medical Device for Delivering Biologically Active Material with Desired Distribution

1.1 Non-Structural Elements

Even if a biologically active material having a pharmacological effect is delivered to a body tissue, such effect may not result if the concentration of the biologically active material in the body tissue is below a certain concentration

($C_{min}$). On the other hand, a biologically active material becomes toxic if its concentration is higher than a certain concentration ($C_{max}$). The concentration of the biologically active material at each and every area throughout the body tissue to be treated should be at or above $C_{min}$ but at or under $C_{max}$ of the biologically active material.

When the medical device is comprised of a plurality of struts comprising a biologically active material, the body tissue located at or near a center of each "cell" of the medical device, i.e., openings between the struts, tends to have the lowest concentration of the biologically active material. Such concentration can be below $C_{min}$. This is particularly true when the biologically active material is hydrophobic. When the concentration of the biologically active material in the tissue located at the center of each cell is lower than $C_{min}$, the concentration can be increased by increasing the amount of the biologically active material coated on outer surface of each strut. However, then the concentration at the tissue adjacent to the struts may exceed $C_{max}$.

For example, FIG. **1** depicts a coated stent **10** having a conventional geometric pattern, which is placed in a blood vessel **15** having a vessel wall **12** to be treated. The biologically active material coated on struts **13** of the stent **10** is released into the vessel wall **12** to be treated. FIGS. **2**A and **2**B show cross sectional views along line A-A and line B-B (shown in FIG. **2**A) of the stent **10** in FIG. **1** and the concentration levels of the biologically active material in each area surrounding the struts **13** at a certain time after the stent **10** was inserted into the blood vessel **15**. The area adjacent to the struts, i.e., the area between the struts **13** and line **16** has a concentration level at or below $C_{max}$, which is just below the toxic level. The farther from the struts **13** the area is located, the lower the concentration becomes. Thus, the concentration levels gradually decrease from the area between lines **16** and **17**, the area between **17** and **18**, to between **18** and **19**. The area between line **18** and line **19** has a concentration level at or higher than $C_{min}$. A concentration of the biologically active material in the area outside line **19** is below $C_{min}$, and thus the pharmacological effects of the biologically active material does not result in the area.

Furthermore, FIGS. **2**A and **2**B clearly show that there are gaps between each strut **13**, i.e., near the center of cells, wherein the vessel wall to be treated does not receive sufficient biologically active material to have $C_{min}$. The size of the area within line **19**, i.e., the areas having the concentrations above $C_{min}$, may be increased to include the entire area of the vessel wall **12** to be treated if the amount of the biologically active material on the struts **13** is increased. However, by doing so, the area adjacent to the struts **13** may be also increased and exceed the toxic level. Therefore, there is a need for a medical device that can ensure the concentration of the biologically active material throughout the body tissue to be treated is at least $C_{min}$ and at most $C_{max}$.

To achieve such a desired distribution of a biologically active material throughout the body tissue to be treated, the embodiments of the medical device of the present invention comprise a plurality of struts and a plurality of non-structural elements integral to the struts. The struts and non-structural elements comprise the biologically active material. These non-structural elements are used to adjust the distribution of the biologically active material in the body tissue so that the desired concentration-profile for the biologically active material released from the medical device into the body tissue can be achieved. For instance, the medical device of the present invention can achieve concentrations higher than $C_{min}$ at the tissue located at the center of cells without increasing the local concentration at an area adjacent to the struts higher than $C_{max}$.

An example is shown in FIGS. **3**, **4**A and **4**B. FIG. **3** depicts a coated stent **10** which is obtained by modifying the conventional geometric pattern of stent **10** shown in FIG. **1** by incorporating non-structural elements **14** integral to the struts **13**. The stent **10** is placed in a blood vessel **15** having a vessel wall **12** to be treated. The biologically active material coated on struts **13** and non-structural elements **14** of the stent **10** is released into the vessel wall **12** to be treated and tissue **12***a* surrounding the vessel wall **12**. FIGS. **4**A and **4**B show cross sectional views along line C-C and D-D (shown in FIG. **4**A) of the stent **10** in FIG. **3** and the concentration levels of the biologically active material in each area surrounding the struts **13** and the nonstructural elements **14** at a certain time after the stent **10** was inserted in the blood vessel **15**. The area adjacent to the struts, i.e., the area between the struts **13** or the nonstructural elements **14** and line **16** has a concentration level from at or below $C_{max}$, which is just below the toxic level. The farther from the struts **13** or the nonstructural elements **14** the area is located, the lower the concentration becomes. The area between line **18** and line **19** has the concentration level at or higher than $C_{min}$. FIG. **4**A clearly shows that the stent **10** can achieve concentrations higher than $C_{min}$ throughout the entire area of the vessel wall **12** to be treated, even at areas located at the center of cells, without increasing the concentration at areas adjacent to the struts above $C_{max}$.

The term "non-structural element" refers to an element integral with a strut, which can project from the strut or can be located along the strut. Such non-structural elements have substantially no effect on the mechanical properties of the struts, such as, for example, (1) radial strength, (2) longitudinal flexibility, (3) expansion ratio, (4) trackability and (5) profile of a medical device comprising the plurality of struts. In embodiments of the medical device of the present invention, the non-structural elements are integral with the struts, namely, they are generally made from the same material as the struts and are formed as a continuous part of the struts. Preferably, the non-structural elements and struts may be manufactured simultaneously; for example, struts having non-structural elements can be laser-ablated from a plate of metal or polymer.

FIG. **5** depicts example of conventional struts without non-structural element, and FIGS. **6**-**14** depict examples of non-structural elements integral with the conventional struts. Shapes of the non-structural elements include, but not limited to, a straight rod (**21** in FIG. **6**), a cone (**22** in FIG. **7**), a truncated cone (not shown), a hoop (**23** in FIG. **8**), a knot (**24** in FIG. **9**), a bent rod (**25** in FIG. **10**), an oval (**26** in FIG. **11**), and a rod having heads at its ends (**27** in FIGS. **12** and **28** in FIG. **13**). Bends in the struts (**29***a* and **29***b* in FIG. **14**) can be used as non-structural elements so long as they do not affect the mechanical properties of the struts.

This embodiment of the medical device of the present invention can be used for delivering any kind of biologically active material. Preferably, the biologically active material is hydrophobic, e.g., paclitaxel, actinomycin, sirolimus, tacrolimus, everolimus, dexamethasone, halofuginone and hydrophobic nitric oxide adducts. Other examples of the biologically active material, coatings containing the biologically active material, and examples of the medical device are explained later in this application.

1.2 Designing Medical Devices Having Struts and Non-Structural Elements

The present invention is directed to a method for designing a medical device comprising a plurality of struts and

non-structural elements integral with the struts for delivering a biologically active material to a body tissue of a patient. As explained above, when the struts are placed in a certain geometric pattern, the concentration of a biologically active material at a center of each cell may not reach $C_{min}$ of the biologically active material. However, the method of the present invention provides a geometric pattern of the struts in which the concentration of a biologically active material above $C_{min}$ can be achieved throughout the body tissue to be treated without increasing the concentration at the tissue located adjacent to the struts above $C_{max}$.

In the method of the invention, a preliminary medical device comprising a plurality of struts in a geometric pattern is modified by incorporating non-structural elements to the struts to improve the concentration-profile for the biologically active material released from the device to the body tissue to be treated. Any medical device comprising a plurality of struts in a geometric pattern, such as stent, can be used as a preliminary medical device for the method of the invention provided that the struts comprise a biologically active material.

In the method of the present invention, a concentration-profile for the biologically active material delivered to the body tissue from the preliminary medical device is determined. From this profile, the areas of tissue in which the concentration of the biologically active material is below $C_{min}$ can be determined. Such areas are then correlated to the parts of the geometric pattern of the struts of the preliminary medical device that were in contact with or near such areas.

The determination of such concentration-profile can be conducted by actually measuring concentrations using the biologically active material in vitro with a tissue model, which is similar to the body tissue to be treated, such as cannulated animal arteries with surrounding tissue or an artificial tissue, or in vivo with an animal model, such as rabbits or pigs. The biologically active material used for the experiment may be labeled with a fluorescence, a radioactive material or dye. Such labeled biologically active material is coated on the medical device, and then the coated medical device is inserted into the tissue model, or artificial tissue, or implanted in an animal. Alternatively, the biologically active material may be detected using standard GLP separation, mass spectroscopy or other direct analytical methods. After insertion, the tissue may be appropriately sectioned, and the concentration-profile for the labeled biologically active material is measured by a means appropriate to the label employed for the experiment. However, a necessary care should be taken that the label would not greatly affect the diffusion of the biologically active material itself.

However, the concentration-profile may also be determined by mathematical simulation. For example, assuming a simple diffusion model, such simulation can be conducted by using the following conditions and equations:

$$\frac{\partial C}{\partial t} = D_x\left(\frac{\partial^2 C}{\partial x^2}\right) + D_z\left(\frac{\partial^2 C}{\partial z^2}\right)$$

wherein C refers to a concentration of the biologically active material in the body tissue, x refers to a distance from the medical device along x axis which is perpendicular to a boundary between the medical device and the body tissue, z refers to a distance from the medical device along z axis which is parallel to the boundary, Dx refers to a diffusion coefficient of the biologically active material in direction along x axis, Dz refers to a diffusion coefficient of the biologically active material in a direction along z axis. For example, such x axis and z axis are shown in FIGS. **1**, **2B**, **3** and **4B**. Dx and Dz can be determined by the experiments using the labeled biologically active material in vitro or in vivo as described above. C=0 at t=0, wherein boundary conditions are as follows:

(i) at a common boundary between the struts and the body tissue (at x=0):

$$D_x\frac{\partial C}{\partial x} = h_1(C - C_T)$$

wherein $C_T$ refers to a concentration of the biologically active material in the struts, and $h_1$ refers to a mass transfer coefficient. Value of $h_1$ can be determined by the same experiments described above or determined by assumption based on the information known to one skilled in the art;

(ii) at a boundary between blood flow and the body tissue (at x=0):

$$D_x\frac{\partial C}{\partial x} = h_2(C - 0)$$

wherein $h_2$ refers to another mass transfer coefficient. Value of $h_2$ can be determined by the same experiment mentioned above or determined by assumption based on the information known to one skilled in the art;

(iii) at an adventitial side of vascular wall (at x=L):

$$D_x\frac{\partial C}{\partial x} = -h_3(C - 0)$$

wherein $h_3$ is yet another mass transfer coefficient, and L is a width of a region of interest. Value of $h_3$ can be determined by the same experiment mentioned above or determined by assumption based on the information known to one skilled in the art; and

(iv) "symmetry" (no-flux) boundary conditions at certain cross-sections perpendicular to z axis:

$$\frac{\partial C}{\partial z}(z = 0) = \frac{\partial C}{\partial z}(z = L_z) = 0$$

wherein Lz is the length along z axis of a region of interest.

Although a simplified model based on two diffusion coefficients of the biologically active material in two directions, i.e., depth of the tissue penetration and the distance diffused, is described above as an example, there are more complex models which can be also employed for the method of the present invention. Such complex models may further account for other variables, such as convection, vessel wall inhomogeneties, the type of cells, the lesions, the variabilities brought by different coatings or coating porosity, blood flow, body temperature, blood pressure, and/or pressure of the implant against the vessel wall.

Subsequent to determining the concentration-profile for the biologically active material which is released from the

preliminary medical device, the geometric pattern of the preliminary medical device is modified by incorporating a plurality of non-functional elements that are integral with the struts to achieve more desired distribution of the biologically active material in the body tissue to be treated. The non-structural elements also comprise the biologically active material. For example, the area of tissue in which the concentration of the biologically active material is below $C_{min}$ is determined from the concentration-profile. Then, it is determined which parts of the geometric pattern of the struts of the preliminary medical device were in contact with or near such areas. The non-structural elements can be incorporated near such parts in the geometric pattern, so that the biologically active material released from the non-structural elements would change the concentration in those areas.

For example, a stent **10** having a plurality of struts **13** in a conventional geometric pattern in FIG. **1** can be provided as the preliminary medical device. The struts **13** are coated with a biologically active material. Then, a concentration-profile in a body tissue for the biologically active material which is released from the struts **13** is determined. An example of such profile is shown in FIGS. **2**A and **2**B with the cross-sectional views of the stent **10** in the blood vessel **15**. The determination of such concentration-profile can be conducted by actually measuring concentrations or by mathematical simulation as mentioned above. According to the obtained concentration-profile, the geometric pattern of the struts **13** of the preliminary stent **10** are modified with non-structural elements **14**, for example, as shown in FIG. **3**. FIGS. **4**A and **4**B show the concentration-profile views for the biologically active material in the vessel wall **12**. When the concentration-profile in the vessel wall **12** to be treated shown in FIGS. **2**A-B and **4**A-B are compared, in FIGS. **4**A-B, the concentrations generally throughout the entire area of the vessel wall **12** to be treated are above $C_{min}$ and below $C_{max}$. It is clear that the modified stent **10** achieves a more desirable concentration-profile in the vessel wall **12** to be treated with the biologically active material than the preliminary stent **10**.

Preferably, after a concentration-profile for the biologically active material in the body tissue which is released from the modified preliminary medical device is determined, if there is an area of the body tissue having the local concentration of the biologically active material lower than $C_{min}$, then the device is modified again by adding non-structural elements to the struts. In addition to or instead of merely adding additional non-structural elements, the non-structural elements which have been already added can be removed or relocated according to the determined concentration-profile. Consequently, a medical device having further improved delivery of the biologically active material is obtained. If necessary, the determination step and the modification step explained above can be repeated as many as possible.

1.3 Medical Device with Radially Asymmetric Area Having Non-Structural Elements

The prior sections (section 1.1 and 1.2) explained how non-structural elements can be added to a preliminary medical device to achieve a more desired concentration-profile for the biologically active material released from the device into body tissue. When the entire outer surface of a medical device, which comprises the plurality of struts and non-structural elements, is used to treat body, the non-structural elements should be positioned uniformly throughout the entire outer surface of the medical device.

However, if the body tissue to be treated is smaller in surface area than the entire outer surface of the medical device, then the non-structural elements do not have to be positioned throughout the entire surface of the medical device. For example, the medical device can comprise a tubular portion comprising an outer surface, such as a stent, which comprises a plurality of struts and a plurality of non-structural elements. The non-structural elements located in a radially asymmetric distribution, such as shown in FIG. **17** where **33** represents the location of the non-structural element on outer surface of a simplified figure of a stent **32**. In this figure, the non-structural elements are distributed only in a rectangular portion of the outer surface. FIG. **18** depicts a perspective view of a stent **34** wherein non-structural elements **36** are provided onto the struts **35** only in a rectangular portion of the outer surface. Such rectangular portion may be parallel to longitudinal axis of the tubular portion and may have the same length as that of the tubular portion. The rectangular portion is preferably from about 25% to about 75% of the entire outer surface.

The present invention is also directed to a method for delivering a biologically active material to body tissue using the above-mentioned medical device, which comprises a tubular portion comprising an outer surface which comprises a plurality of struts and a plurality of non-structural elements, and the non-structural elements are located in a radially asymmetric distribution on the outer surface. In the method, the medical device is inserted into the body of the patient. Preferably, the non-structural elements are distributed only in a rectangular portion of the outer surface, and the medical device is inserted in such a way that the rectangular portion is in direct contact with the body tissue to be treated. In this way, the body tissue to be treated will receive desired distribution of the biologically active material. On the other hand, the body tissue which does not need to be treated will be exposed to a lesser amount of the biologically active material.

2. Increased Capacity of the End Sections for Carrying or Containing a Biologically Active Material

In other embodiments of the medical device insertable into the body of a patient of the invention, the medical device comprises an outer surface comprising a plurality of struts, and the end sections of the outer surface have a greater capacity per unit length of the outer surface for carrying or containing a biologically active material than the middle section of the outer surface. Specifically, in one embodiment of the medical device, each strut at the end sections has greater available surface area per unit length of the outer surface than the middle section. In another embodiment, the end sections have a greater affinity for the biologically active material per unit length of the outer surface than the middle section.

The medical device of the present invention may be manufactured with or without a biologically active material by a manufacturer. When the medical device of the present invention is manufactured without a biologically active material, a practitioner (e.g., a medical doctor or a nurse) can apply the biologically active material to the medical device. In either case, since the end sections of the outer surface have a greater capacity per unit length of the outer surface for carrying or containing the biologically active material than the middle section, the end sections will carry a greater amount of the biologically active material when the biologically active material is applied to the medical device without needing to change application method of the biologically active material to the end sections and the method to the middle section. Therefore, when a practitioner applies to the outer surface of the medical device, such as by dipping, a coating composition containing a biologically active mate-

rial, a larger amount of the biologically active material per unit length of the outer surface will be deposited at the end sections than the middle section.

The term "unit length of the outer surface" refers to the length on an imaginary straight line along the outer surface drawn between a point on an edge of the outer surface and another point on the opposing edge of the outer surface. Therefore, the terms, such as "capacity per unit length of the outer surface," "available surface area per unit length of the outer surface," and "amount per unit length of the outer surface," refer respectively to the capacity, available surface area and amount per unit length of the imaginary straight line explained above.

2.1 Increased Available Surface Area at the End Sections

As explained above, one of the embodiments of the medical device has end sections which have greater available surface area per unit length of the outer surface than that of the middle section. The term "available surface area" refers to a surface area which is available to be coated by a coating composition comprising a biologically active material.

One way of increasing the available surface area of the end sections is to fabricate the outer surface of the medical device using more material at its ends. For example, when the medical device is comprised of struts, the available surface area per unit length of the outer surface in the end sections is increased by adding non-structural elements to the struts. The non-structural elements are explained above (see section 1.1). The end sections comprise a greater number of the non-structural elements per unit length of the outer surface than the middle section. The middle section may have smaller number of the non-structural elements or no non-structural elements.

Further, the available surface area can be increased by increasing the surface area of the struts themselves. For example, wavy struts **30** shown in FIG. **15** can have more outer surface area per length than straight struts shown in FIG. **5**. Also, struts having greater average diameter, such as struts which are thicker or wider at certain portion **31** shown in FIG. **16**, have greater outer surface area per length than struts which have smaller average diameter. Moreover, the end sections of the outer surface can be made to have greater available surface area by roughing the struts' outer surface or providing indentations or grooves on the struts' surface. The above-mentioned wavy struts, wider or thicker struts, indentations and grooves may have various shapes, so long as such structure does not affect stents structural functions. For example, the above-mentioned structure should not hinder self-expansion of a self-expanding stent and should not cause any harm to the patient body. The above-mentioned wavy struts, indentations and grooves can be manufactured by laser ablation.

In another embodiment in which the capacity of the end sections to carry or contain the biologically active material is greater than the capacity of the middle section, the end sections of the outer surface are more porous, and the middle section of the surface is relatively less porous. The middle section may also be non-porous. For example, in FIG. **19**, the circles **45** and **47** show enlarged portions of the outer surface of the struts **42** of a stent **40** in the middle section **44** and end section **46**, respectively. The surface of the struts in the end section **46** has more pores **48** than the surface of the struts at the middle section **44**. In such embodiment, the end sections **46** have a greater available surface area per unit length of the outer surface than that of the middle section **44** since the pores **48** increase available surface area.

The end sections of the outer surface may be made porous by forming the end sections of the outer surface themselves from a porous material or by forming the end sections with a non-porous material and then covering the end sections with a porous coating layer. For example, porous metal struts can be prepared by sintering metal, i.e., molding or pressing metal particles into a desired shape and heating them to a temperature slightly below the melting point of the metal. Porosity can be changed by using different particle sizes and/or dimensions and/or different temperatures. Also, porous metal struts can be prepared by using metal filaments or fibers. See e.g. U.S. Pat. No. 5,843,172 issued to Yan which discloses examples of struts made of porous materials, which is incorporated herewith by reference.

The end sections of the outer surface may be made porous by coating with a porous coating layer. A porous coating layer may be prepared, for example, by applying a mixture of a polymer, an elutable particulate material and a solvent on a surface to form a layer, and then eluting the elutable particulate material from the layer. The following is a detailed description of suitable materials and methods useful in producing a porous coating layer of the invention.

Polymer(s) useful for forming the porous coating layer should be ones that are biostable, biocompatible, particularly during insertion or implantation of the device into the body and avoids irritation to body tissue. Examples of such polymers include, but not limited to, polyurethanes, polyisobutylene and its copolymers, silicones, and polyesters. Other suitable polymers include polyolefins, polyisobutylene, ethylene-alphaolefin copolymers, acrylic polymers and copolymers, vinyl halide polymers and copolymers such as polyvinyl chloride, polyvinyl ethers such as polyvinyl methyl ether, polyvinylidene halides such as polyvinylidene fluoride and polyvinylidene chloride, polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics such as polystyrene, polyvinyl esters such as polyvinyl acetate; copolymers of vinyl monomers, copolymers of vinyl monomers and olefins such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, ethylene-vinyl acetate copolymers, polyamides such as Nylon 66 and polycaprolactone, alkyd resins, polycarbonates, polyoxyethylenes, polyimides, polyethers, epoxy resins, polyurethanes, rayon-triacetate, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, carboxymethyl cellulose, collagens, chitins, polylactic acid, polyglycolic acid, and polylactic acid-polyethylene oxide copolymers. Since the polymer is being applied to a part of the medical device which undergoes mechanical challenges, e.g. expansion and contraction, the polymers are preferably selected from elastomeric polymers such as silicones (e.g. polysiloxanes and substituted polysiloxanes), polyurethanes, thermoplastic elastomers, ethylene vinyl acetate copolymers, polyolefin elastomers, and EPDM rubbers. The polymer is selected to allow the coating to better adhere to the surface of the expandable portion of the medical device when it is subjected to forces or stress. Furthermore, although the porous coating layer can be formed by using a single type of polymer, various combinations of polymers can be employed.

The elutable particulate materials which can be incorporated into the polymer include, but not limited to, polyethylene oxide, polyethylene glycol, polyethylene oxide/polypropylene oxide copolymers, polyhydroxyethyl methacrylate, polyvinylpyrrolidone, polyacrylamide and its copolymers, salts, e.g., sodium chloride, sugars, and elutable biologically active materials such as heparin. The amount of

elutable particulate material that is incorporated into the polymer should range from about 20% to 90% by weight of the porous coating layer. Furthermore, to increase the porosity of the coating layer applied to the end sections of the surface, a larger amount of the elutable particulate material can be used to form the porous coating layer at the end sections than are used to form the porous coating layer at the middle section. For example, the amount of the elutable particulate material may be from about 0% to about 40% for the porous coating layer covering the middle section, and about 50% to 90% for the porous coating layer covering at the end sections. Also, a more porous coating layer can be realized by using larger average particle size of the elutable material. For example, the particles may have an average particle size from 60-100 microns for porous coating layer covering the end sections and from 0 to about 30 microns for the porous coating layer covering middle section.

The solvent that is used to form the mixture or slurry of polymer and elutable particulate materials include ones which can dissolve the polymer into solution and do not alter or adversely impact the therapeutic properties of the biologically active material employed. Examples of useful solvents for silicone include tetrahydrofuran (THF), chloroform and dichloromethane. The composition of polymer and elutable particulate material can be applied to the portion of the medical device in a variety of ways. For example, the composition can be spray-coated onto the device or the device can be dipped into the composition. One of skill in the art would be aware of methods for applying the coating to the device.

The thickness of the porous coating layer can range from about 25 μm to 0.5 mm. Preferably, the thickness is about 30 μm to 100 μm. After the composition is applied to the device, it should be cured to produce a polymer containing the particulate material and to evaporate the solvent.

To elute the particulate material from the polymer, a solvent is used. The device can be soaked in the solvent to elute the particulate materials. Other methods of eluting the particulate are apparent to those skilled in the art. The choice of the solvent depends upon the solubility of the elutable particulate material in that solvent. For instance, for water-soluble particulate materials such as heparin, water can be used. For elutable particulate materials that can be dissolved in organic solvents, such organic solvents can be used. Examples of suitable solvents, without limitation, include ethanol, dimethyl sulfoxide, etc.

Another example of a method for preparing a porous coating is a catalyst-free vapor deposition of a coating composition comprising a polyamide, parylene or a parylene derivative. See U.S. Pat. No. 6,299,604 to Ragheb et al., which is incorporated herein by reference.

In another embodiment of the present invention, the surface including the end sections and middle section are covered with a same porous coating layer composition, but the porous coating layer is thicker at the end sections than at the middle section. For example, a porous coating layer is applied to the entire surface, and then another porous coating layer is applied to the end sections while the middle section is covered by a sheath. The thickness of the porous coating layer at the end sections may be from about 80 μm to about 0.5 mm, and that at the middle section may be from about 10 μm to 40 μm. Since there is more porous coating at the end sections, the end sections of the outer surface should have a greater capacity to carry or contain a biologically active material.

2.2 The End Sections with Greater Affinity for the Biologically Active Material

In another embodiment of the medical device of the present invention, the end sections of the outer surface have a greater affinity for the biologically active material than the middle section. In particular, the end sections comprise a first matrix material and the middle section comprises a second matrix material. The first matrix material has a greater affinity for the biologically active material of interest than the second matrix material so that the end sections can carry or contain a larger amount of the biologically active material per unit length of the outer surface than the middle section. The end sections and the middle section of the outer surface may be formed from the first matrix material and the second matrix material, respectively. Preferably, the end sections of the outer surface and the middle section of the outer surface are formed of another material and then are covered with a coating comprising each of the matrix materials.

Generally, when a biologically active material used is a hydrophilic, e.g., heparin, then a matrix material comprising a more hydrophilic material has a greater affinity for the biologically active material than another matrix material that is less hydrophilic. When a biologically active material used is a hydrophobic, e.g., paclitaxel, actinomycin, sirolimus (RAPAMYCIN), tacrolimus, everolimus, and dexamethasone, then a matrix material that is more hydrophobic has a greater affinity for the biologically active material than another matrix material that is less hydrophobic.

Examples of suitable hydrophobic polymers include, but not limited to, polyolefins, such as polyethylene, polypropylene, poly(1-butene), poly(2-butene), poly(1-pentene), poly(2-pentene), poly(3-methyl-1-pentene), poly(4-methyl-1-pentene), poly(isoprene), poly(4-methyl-1-pentene), ethylene-propylene copolymers, ethylene-propylene-hexadiene copolymers, ethylene-vinyl acetate copolymers, blends of two or more polyolefins and random and block copolymers prepared from two or more different unsaturated monomers; styrene polymers, such as poly(styrene), poly(2-methylstyrene), styrene-acrylonitrile copolymers having less than about 20 mole-percent acrylonitrile, and styrene-2,2,3,3,-tetrafluoropropyl methacrylate copolymers; halogenated hydrocarbon polymers, such as poly(chlorotrifluoroethylene), chlorotrifluoroethylene-tetrafluoroethylene copolymers, poly(hexafluoropropylene), poly(tetrafluoroethylene), tetrafluoroethylene, tetrafluoroethylene-ethylene copolymers, poly(trifluoroethylene), poly(vinyl fluoride), and poly (vinylidene fluoride); vinyl polymers, such as poly(vinyl butyrate), poly(vinyl decanoate), poly(vinyl dodecanoate), poly(vinyl hexadecanoate), poly(vinyl hexanoate), poly(vinyl propionate), poly(vinyl octanoate), poly(heptafluoroisopropoxyethylene), poly(heptafluoroisopropoxypropylene), and poly(methacrylonitrile); acrylic polymers, such as poly (n-butyl acetate), poly(ethyl acrylate), poly(1-chlorodifluoromethyl)tetrafluoroethyl acrylate, poly di(chlorofluoromethyl)fluoromethyl acrylate, poly(1, 1-dihydroheptafluorobutyl acrylate), poly(1,1-dihydropentafluoroisopropyl acrylate), poly(1,1-dihydropentadecafluorooctyl acrylate), poly(heptafluoroisopropyl acrylate), poly 5-(heptafluoroisopropoxy)pentyl acrylate, poly 11-(heptafluoroisopropoxy)undecyl acrylate, poly 2-(heptafluoropropoxy)ethyl acrylate, and poly(nonafluoroisobutyl acrylate); methacrylic polymers, such as poly(benzyl methacrylate), poly(n-butyl methacrylate), poly(isobutyl methacrylate), poly(t-butyl methacrylate), poly(t-butylaminoethyl methacrylate), poly(dodecyl methacrylate), poly (ethyl methacrylate), poly(2-ethylhexyl methacrylate), poly (n-hexyl methacrylate), poly(phenyl methacrylate), poly(n-propyl methacrylate), poly(octadecyl methacrylate), poly(1, 1-dihydropentadecafluorooctyl methacrylate), poly (heptafluoroisopropyl methacrylate), poly

(heptadecafluorooctyl methacrylate), poly(1-hydrotetrafluoroethyl methacrylate), poly(1,1-dihydrotetrafluoropropyl methacrylate), poly(1-hydrohexafluoroisopropyl methacrylate), and poly(t-nonafluorobutyl methacrylate); polyesters, such a poly (ethylene terephthalate) and poly(butylene terephthalate); condensation type polymers such as and polyurethanes and siloxane-urethane copolymers; polyorganosiloxanes, i.e., polymeric materials characterized by repeating siloxane groups, represented by $R_a SiO_{4-a/2}$, where R is a monovalent substituted or unsubstituted hydrocarbon radical and the value of a is 1 or 2; and naturally occurring hydrophobic polymers such as rubber.

Examples of suitable hydrophilic monomer include, but not limited to, (meth)acrylic acid, or alkaline metal or ammonium salts thereof; (meth)acrylamide; (meth)acrylonitrile; those polymers to which unsaturated dibasic, such as maleic acid and fumaric acid or half esters of these unsaturated dibasic acids, or alkaline metal or ammonium salts of these dibasic adds or half esters, is added; those polymers to which unsaturated sulfonic, such as 2-acrylamido-2-methylpropanesulfonic, 2-(meth)acryloylethanesulfonic acid, or alkaline metal or ammonium salts thereof, is added; and 2-hydroxyethyl(meth)acrylate and 2-hydroxypropyl(meth) acrylate.

Polyvinyl alcohol is also an example of hydrophilic polymer. Polyvinyl alcohol may contain a plurality of hydrophilic groups such as hydroxyl, amido, carboxyl, amino, ammonium or sulfonyl (—$SO_3$). Hydrophilic polymers also include, but are not limited to, starch, polysaccharides and related cellulosic polymers; polyalkylene glycols and oxides such as the polyethylene oxides; polymerized ethylenically unsaturated carboxylic acids such as acrylic, mathacrylic and maleic acids and partial esters derived from these acids and polyhydric alcohols such as the alkylene glycols; homopolymers and copolymers derived from acrylamide; and homopolymers and copolymers of vinylpyrrolidone.

The first matrix material and the second matrix material may be prepared using either a hydrophilic polymer or a hydrophobic polymer, or a blend of a hydrophobic polymer and a hydrophilic polymer in a chosen ratio. For example, when the biologically active material is hydrophilic, then the first matrix material may be prepared by blending from about 55% to about 100% hydrophilic polymer and from about 45% to about 0% hydrophobic polymer; and the second matrix material may be prepared by blending from about 55% to about 100% hydrophobic polymer and from about 45% to about 0% hydrophilic polymer. The first matrix material contains a greater amount of the hydrophillic polymer than the second matrix material. When the biologically active material is hydrophobic, then the first matrix material may be prepared by blending from about 55% to about 95% hydrophobic polymer and from about 45% to about 5% hydrophilic polymer; and the second matrix material may be prepared by blending from about 55% to about 95% hydrophilic polymer and from about 45% to about 5% hydrophobic polymer. The first matrix material contains a greater amount of the hydrophobic polymer than the second matrix material.

Again, the outer surface of the medical device of the present invention is, covered with each matrix material, i.e., the end sections with a first matrix material and the middle section with a second matrix material. A first matrix material composition may be prepared and applied by any method to a surface of a medical device to form a coating, such as spraying, dipping, rolling, and electrostatic deposition. Likewise, a second matrix material composition may be prepared and applied by such methods. The first matrix material composition may be applied to the end sections of the outer surface while the middle section is covered to prevent coating the middle section with the first matrix material. Then the second matrix material composition may be applied to the middle section while the end sections are covered. In another embodiment, the second material composition may be applied to the entire outer surface including the middle section and the end sections, then the first matrix material composition may be applied to the end sections while the middle section is covered.

After the matrix material compositions are applied to the outer surface, the surface should be cured to produce matrix material coatings. The thickness of the matrix material coating can range from about 25 μm to about 0.5 mm. Preferably, the thickness is about 30 μm to 100 μm.

2.3 The End Sections with Greater Amount of Chemical Linking Material to Carry or Contain the Biologically Active Material

In yet another embodiment of the present invention, the capacity of the end sections of the outer surface for carrying or containing a biologically active material can be increased relative to that of the middle section by using an increased amount of chemical linking material to link the biologically active material to the end sections of the outer surface. Specifically, the middle section and end sections of the outer surface are covered with a chemical linking material, and the end sections carry or contain a larger amount of the linking material per unit length of outer surface than the middle section. The chemical linking material allows the biologically active material to attach to the outer surface. "Linking materials" may be any material which can be coupled to a biologically active material by any bond that are known in the relevant art including, but not limited to, Van der Waals force, ionic bond, covalent bond, hydrogen bond or chemical cross-linking.

For example, U.S. Pat. No. 5,356,433 to Rowland et al., discloses that polysaccharides can be immobilized onto metallic surfaces by applying an organosilane coating with amine functionality and then applying a polysaccharide using carbodiimide as a coupling agent. In the present invention, if the organosilane with amine functionality is used as a linking material, the amount of this material per unit length of the outer surface at the end sections is greater than that at the middle section. In that way, a larger amount of a polysaccharide, which is a biologically active material, can be coupled to the end sections.

Also, U.S. Pat. No. 5,336,518 to Narayanan et al. discloses that a polysaccharide can be immobilized on a surface by applying a coat of heptafluorobutylmethacrylate (HFBMA) by radiofrequency (RF) plasma deposition, creating functional groups on the surface by RF plasma with water vapor, and then applying the polysaccharide using carbodiimide. In the present invention, a larger amount of HFBMA, a linking material, is applied to the end sections so that larger amount of a polysaccharide, a biologically active material can be coupled to the HFBMA.

3. Radially Asymmetric Medical Devices Having Increased Capacity for Carrying or Containing a Biologically Active Material

3.1 Medical Devices Having Non-Structural Elements Located in a Radially Asymmetric Distribution

As explained above, one way to increase the capacity for carrying or containing a biologically active material of the medical device is to increase available surface area. In one embodiment of the medical device of the invention, the available surface area is increased in radially asymmetric

manner along the entire outer surface, instead of only at the end sections. One such embodiment where the surface area is increased in a radially asymmetric manner by adding non-structural elements to the outer surface (as to non-structural elements, see section 1.3). For example, only a rectangular portion of the outer surface has the non-structural elements. Such rectangular portion may be parallel to longitudinal axis of the tubular portion and may have the same length as that of the tubular portion. The rectangular portion is preferably from about 25% to about 75% of the entire outer surface. Please see section 1.3 as to a method for delivering a biologically active material to body tissue using such medical device.

3.2 Medical Device Having Radially Asymmetric Increased Available Surface Area or Affinity

Another embodiment of the medical device of the invention comprises a tubular portion comprising struts and having an outer surface. A portion of the outer surface has increased available surface or affinity for the biologically active material in such a way that the available surface area or affinity for the biologically active material is radially asymmetric. Please see prior section (section 3.1) as to examples of radially asymmetric distributions. Increased available surface area or increased affinity to the biologically active material can be achieved as explained in the prior sections (sections 2.1 and 2.2). Please see section 1.3 as to a method for delivering a biologically active material to body tissue using such medical device.

4. Suitable Medical Devices

The medical devices of the present invention are insertable into the body of a patient. Namely, at least a portion of such medical devices may be temporarily inserted into or semi-permanently or permanently implanted in the body of a patient. Preferably, the medical devices of the present invention comprise a tubular portion which is insertable into the body of a patient. The tubular portion of the medical device need not to be completely cylindrical. For instance, the cross-section of the tubular portion can be any shape, such as a rectangle, a triangle, etc., not just a circle.

The medical devices suitable for the present invention include, but are not limited to, stents, surgical staples, catheters, such as central venous catheters and arterial catheters, guidewires, balloons, filters (e.g., vena cava filters), cannulas, cardiac pacemaker leads or lead tips, cardiac defibrillator leads or lead tips, implantable vascular access ports, stent grafts, vascular grafts or other grafts, interluminal paving system, intra-aortic balloon pumps, heart valves, cardiovascular sutures, total artificial hearts and ventricular assist pumps.

Medical devices which are particularly suitable for the present invention include any kind of stent for medical purposes, which are known to the skilled artisan. Suitable stents include, for example, vascular stents such as self-expanding stents and balloon expandable stents. Examples of self-expanding stents useful in the present invention are illustrated in U.S. Pat. Nos. 4,655,771 and 4,954,126 issued to Wallsten and 5,061,275 issued to Wallsten et al. Examples of appropriate balloon-expandable stents are shown in U.S. Pat. No. 4,733,665 issued to Palmaz, U.S. Pat. No. 4,800,882 issued to Gianturco, U.S. Pat. No. 4,886,062 issued to Wiktor and U.S. Pat. No. 5,449,373 issued to Pinchasik et al. A bifurcated stent is also included among the medical devices suitable for the present invention.

The medical devices suitable for the present invention may be fabricated from polymeric and/or metallic materials. Examples of such polymeric materials include polyurethane and its copolymers, silicone and its copolymers, ethylene vinyl-acetate, poly(ethylene terephthalate), thermoplastic elastomer, polyvinyl chloride, polyolephines, cellulosics, polyamides, polyesters, polysulfones, polytetrafluoroethylenes, acrylonitrile butadiene styrene copolymers, acrylics, polyactic acid, polyclycolic acid, polycaprolactone, polyacetal, poly(lactic acid), polylactic acid-polyethylene oxide copolymers, polycarbonate cellulose, collagen and chitins. Examples of suitable metallic materials include metals and alloys based on titanium (e.g., nitinol, nickel titanium alloys, thermo-memory alloy materials), stainless steel, platinum, tantalum, nickel-chrome, certain cobalt alloys including cobalt-chromium-nickel alloys (e.g., Elgiloy® and Phynox®) and gold/platinum alloy. Metallic materials also include clad composite filaments, such as those disclosed in WO 94/16646.

The medical devices suitable for the present invention also have an outer surface, and the outer surface has end sections and middle section. The term "outer surface" refers to a surface of the medical devices which are to be exposed to the body tissue. For example, the tubular structure shown in FIG. **20** is a simplified view of a stent **40**. The outer surface of the stent is the surface that is in direct contact with the body tissue when the device is inserted into the body. In the case that the medical device is a stent **40** comprised of struts **42** as shown in FIG. **19**, the "outer surface" of the stent refers to the surfaces of the struts which are to directly contact with the body lumen or tissue.

The term "end section" of the outer surface refers to that part of the surface which extends from an end or edge of the tubular portion up to about 25%, preferably from about 3% to about 20% of the entire length of the outer surface. For example, when the medical device is a stent **40** as shown in FIG. **19** or **20**, the end section **46** of the outer surface is a ring-shape portion extending from the edge of the outer surface of stent having length e, which is up to 25% of the entire length a of the outer surface of stent. In FIGS. **19** and **20**, the end sections **46** are shown as the shaded portions.

The term "middle section" refers to the remainder of the outer surface that is surrounded by the end sections as defined above. For example, in FIG. **19** or **20**, the middle section **44** is a ring-shape portion having length m, which is surrounded by the end sections.

5. Applying Biologically Active Material to the Outer Surface

As discussed earlier, the biologically active material can be applied to the embodiments described in sections 2.1 to 2.3 when the device is manufactured or afterwards by a medical professional shortly before the device is inserted into a patient. The biologically active material may be applied to the outer surface of the device obtained as in sections 1.1-1.3, 2.1-2.3 and 3.1-3.2, alone or in conjunction with other materials, such as a polymeric material. For example, in the embodiment where the end sections have a greater available surface area per unit length of the outer surface than the middle section, the biologically active material can be applied to the outer surface in a coating composition containing the biologically active material and a polymeric material. Specifically, a coating composition of biologically active material and polymeric material can be prepared and then applied to the outer surface. However, the biologically active material alone can also be applied to the outer surface of this embodiment.

In the embodiments where a portion of the outer surface has a greater affinity for the biologically active material or where a portion of the outer surface contains more chemical liking material, the biologically active material is preferably applied alone to the outer surface. For instance, in the

embodiment having a matrix material with greater affinity for the biologically active material in a portion of the outer surface, the biologically active material can be applied to the matrix material coatings on the outer surface. However, the biologically active material can also be applied to the material along with a polymeric material. Also, the biologically active material can be incorporated into the matrix material coating compositions to form matrix material coatings already containing the biologically active material.

5.1 Coating Compositions and Coating Layers

The coating compositions suitable for the present invention can be applied by any method to a surface of a medical device to form a coating. Examples of such methods are spraying, dipping, rolling, electrostatic deposition and all modern chemical ways of immobilization of bio-molecules to surfaces.

The coating composition used in the present invention may be a solution of a biologically active material in an aqueous or organic solvent. Such coating composition may be applied to a surface, and the solvent may be evaporated. A biologically active material solution may be used when the tubular portion of the medical device has end sections having increased surface area or increased affinity as explained above, especially when the end sections are porous.

Furthermore, coating compositions useful for the present invention may include a polymeric material and optionally a biologically active material dispersed or dissolved in a solvent suitable for the medical device which is known to the skilled artisan. The solvents used to prepare coating compositions include ones which can dissolve the polymeric material into solution and do not alter or adversely impact the therapeutic properties of the biologically active material employed. For example, useful solvents for silicone include tetrahydrofuran (THF), chloroform, toluene, acetone, isooctane, 1,1,1-trichloroethane, dichloromethane, and a mixture thereof.

A coating of a medical device of the present invention may consist of various kinds of combination of multiple coating layers. For example, the first layer and the second layer may contain different biologically active materials. Alternatively, the first layer and the second layer may contain an identical biologically active material having different concentrations. In one embodiment, either of the first layer or the second layer may be free of biologically active material. For example, when the biologically active solution is applied onto a surface and dried (the first layer), a coating composition free of a biologically active material (the second layer) can be applied over the dried biologically active material.

The polymeric material should be a material that is biocompatible and avoids irritation to body tissue. Examples of the polymeric materials used in the coating composition of the present invention include, but not limited to, polycarboxylic acids, cellulosic polymers, including cellulose acetate and cellulose nitrate, gelatin, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, polyanhydrides including maleic anhydride polymers, polyamides, polyvinyl alcohols, copolymers of vinyl monomers such as EVA, polyvinyl ethers, polyvinyl aromatics, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters including polyethylene terephthalate, polyacrylamides, polyethers, polyether sulfone, polycarbonate, polyalkylenes including polypropylene, polyethylene and high molecular weight polyethylene, halogenated polyalkylenes including polytetrafluoroethylene, polyurethanes, polyorthoesters, proteins, polypeptides, silicones, siloxane polymers, polylactic acid, polyglycolic acid, polycaprolactone, polyhydroxybutyrate valerate, styrene-isobutylene copolymers and blends and copolymers thereof. Also, other examples of such polymers include polyurethane (BAYHDROL®, etc.) fibrin, collagen and derivatives thereof, polysaccharides such as celluloses, starches, dextrans, alginates and derivatives, hyaluronic acid, and squalene. Further examples of the polymeric materials used in the coating composition of the present invention include other polymers which can be used include ones that can be dissolved and cured or polymerized on the medical device or polymers having relatively low melting points that can be blended with biologically active materials. Additional suitable polymers include, thermoplastic elastomers in general, polyolefins, polyisobutylene, ethylene-alphaolefin copolymers, acrylic polymers and copolymers, vinyl halide polymers and copolymers such as polyvinyl chloride, polyvinyl ethers such as polyvinyl methyl ether, polyvinylidene halides such as polyvinylidene fluoride and polyvinylidene chloride, polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics such as polystyrene, polyvinyl esters such as polyvinyl acetate, copolymers of vinyl monomers, copolymers of vinyl monomers and olefins such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS (acrylonitrile-butadiene-styrene) resins, ethylene-vinyl acetate copolymers, polyamides such as Nylon 66 and polycaprolactone, alkyd resins, polycarbonates, polyoxymethylenes, polyimides, epoxy resins, rayon-triacetate, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, carboxymethyl cellulose, collagens, chitins, polylactic acid, polyglycolic acid, polylactic acid-polyethylene oxide copolymers, EPDM (etylene-propylene-diene) rubbers, fluorosilicones, polyethylene glycol, polysaccharides, phospholipids, and combinations of the foregoing.

Preferred is polyacrylic acid, available as HYDROPLUS® (Boston Scientific Corporation, Natick, Mass.), and described in U.S. Pat. No. 5,091,205, the disclosure of which is hereby incorporated herein by reference. In a most preferred embodiment of the invention, the polymer is a copolymer of polylactic acid and polycaprolactone.

More preferably for medical devices which undergo mechanical challenges, e.g. expansion and contraction, the polymeric materials should be selected from elastomeric polymers such as silicones (e.g. polysiloxanes and substituted polysiloxanes), polyurethanes, thermoplastic elastomers, ethylene vinyl acetate copolymers, polyolefin elastomers, and EPDM rubbers. Because of the elastic nature of these polymers, the coating composition adheres better to the surface of the medical device when the device is subjected to forces, stress or mechanical challenge.

A controlled-release coating of a biologically active material may be prepared by a coating composition comprising an appropriate hydrophobic polymer. For example, a controlled-release coating may comprise a coating layer containing a biologically active material and a top coating layer comprising a hydrophobic polymer. Also, a controlled-release coating may be prepared from a coating composition containing a mixture of a hydrophobic polymer and a biologically active material.

The amount of the polymeric material present in the coatings can vary based on the application for the medical device. One skilled in the art is aware of how to determine the desired amount and type of polymeric material used in the coating. The thickness of the coating is not limited, but generally ranges from about 25 μm to about 0.5 mm. Preferably, the thickness is about 30 μm to 100 μm.

5.2 Suitable Biologically Active Material

The term "biologically active material" encompasses therapeutic agents, such as drugs, and also genetic materials and biological materials. The genetic materials mean DNA or RNA, including, without limitation, of DNA/RNA encoding a useful protein stated below, anti-sense DNA/RNA, intended to be inserted into a human body including viral vectors and non-viral vectors. Examples of DNA suitable for the present invention include DNA encoding:

anti-sense RNA;

tRNA or rRNA to replace defective or deficient endogenous molecules;

angiogenic factors including growth factors, such as acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factor α and β, platelet-derived endothelial growth factor, platelet-derived growth factor, tumor necrosis factor α, hepatocyte growth factor and insulin like growth factor;

cell ccle inhibitors including CD inhibitors;

thymidine kinase ("TK") and other agents useful for interfering with cell proliferation; and

the family of bone morphogenic proteins ("BMP's") as explained below.

Viral vectors include adenoviruses, gutted adenoviruses, adeno-associated virus, retroviruses, alpha virus (Semliki Forest, Sindbis, etc.), lentiviruses, herpes simplex virus, ex vivo modified cells (e.g., stem cells, fibroblasts, myoblasts, satellite cells, pericytes, cardiomyocytes, sketetal myocytes, macrophage), replication competent viruses (e.g., ONYX-015), and hybrid vectors. Non-viral vectors include artificial chromosomes and mini-chromosomes, plasmid DNA vectors (e.g., PCOR), cationic polymers (e.g., polyethyleneimine, polyethyleneimine (PEI)) graft copolymers (e.g., polyether-PEI and polyethylene oxide-PEI), neutral polymers PVP, SP 1017 (SUPRATEK), lipids or lipoplexes, nanoparticles and microparticles with and without targeting sequences such as the protein transduction domain (PTD).

The biological materials include cells, yeasts, bacteria, proteins, peptides, cytokines and hormones. Examples for peptides and proteins include growth factors (FGF, FGF-1, FGF-2, VEGF, Endotherial Mitogenic Growth Factors, and epidermal growth factors, transforming growth factor α and β, platelet derived endothelial growth factor, platelet derived growth factor, tumor necrosis factor α, hepatocyte growth factor and insulin like growth factor), transcription factors, proteinkinases, CD inhibitors, thymidine kinase, and bone morphogenic proteins (BMP's), such as BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 (Vgr-1), BMP-7 (OP-1), BMP-8. BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, and BMP-16. Currently preferred BMP's are BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7. Alternatively or in addition, molecules capable of inducing an upstream or downstream effect of a BMP can be provided. Such molecules include any of the "hedgehog" proteins, or the DNA's encoding them. These dimeric proteins can be provided as homodimers, heterodimers, or combinations thereof, alone or together with other molecules. Cells can be of human origin (autologous or allogeneic) or from an animal source (xenogeneic), genetically engineered, if desired, to deliver proteins of interest at the transplant site. The delivery media can be formulated as needed to maintain cell function and viability. Cells include whole bone marrow, bone marrow derived mono-nuclear cells, progenitor cells (e.g., endothelial progentitor cells), stem cells (e.g., mesenchymal, hematopoietic, neuronal), pluripotent stem cells, fibroblasts, macrophage, and satellite cells.

Biologically active material also includes non-genetic therapeutic agents, such as:

- anti-thrombogenic agents such as heparin, heparin derivatives, urokinase, and PPack (dextrophenylalanine proline arginine chloromethylketone);
- anti-proliferative agents such as enoxaprin, angiopeptin, or monoclonal antibodies capable of blocking smooth muscle cell proliferation, hirudin, and acetylsalicylic acid, tacrolimus, everolimus, amlodipine and doxazosin;
- anti-inflammatory agents such as glucocorticoids, betamethasone, dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, rosiglitazone, mycophenolic acid, and mesalamine;
- immunosuppressants such as sirolimus (RAPAMYCIN), tacrolimus, everolimus and dexamethasone;
- antineoplastic/antiproliferative/anti-miotic agents such as paclitaxel, 5-fluorouracil, cisplatin, vinblastine, cladribine, vincristine, epothilones, methotrexate, azathioprine, halofuginone, adriamycin, actinomycin and mutamycin; endostatin, angiostatin and thymidine kinase inhibitors, and its analogs or derivatives;
- anesthetic agents such as lidocaine, bupivacaine, and ropivacaine;
- anti-coagulants such as D-Phe-Pro-Arg chloromethyl keton, an RGD peptide-containing compound, heparin, antithrombin compounds, platelet receptor antagonists, anti-thrombin anticodies, anti-platelet receptor antibodies, aspirin (aspirin is also classified as an analgesic, antipyretic and anti-inflammatory drug), dipyridamole, protamine, hirudin, prostaglandin inhibitors, platelet inhibitors and antiplatelet agents such as trapidil or liprostin, tick antiplatelet peptides;
- DNA demethylating drugs such as 5-azacytidine, which is also categorized as a RNA or DNA metabolite that inhibit cell growth and induce apoptosis in certain cancer cells;
- vascular cell growth promotors such as growth factors, Vascular Endothelial Growth Factors (FEGF, all types including VEGF-2), growth factor receptors, transcriptional activators, and translational promotors;
- vascular cell growth inhibitors such as antiproliferative agents, growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin;
- cholesterol-lowering agents; vasodilating agents; and agents which interfere with endogenous vasoactive mechanisms;
- anti-oxidants, such as probucol;
- antibiotic agents, such as penicillin, cefoxitin, oxacillin, tobranycin;
- angiogenic substances, such as acidic and basic fibrobrast growth factors, estrogen including estradiol (E2), estriol (E3) and 17-Beta Estradiol;
- drugs for heart failure, such as digoxin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors including captopril and enalopril, statins and related compounds; and
- macrolides such as sirolimus or everolimus.

Also, the biologically active materials of the present invention include nitric oxide adducts, which prevent and/or treat adverse effects associated with use of a medical device in a patient, such as restenosis and damaged blood vessel

surface. Typical nitric oxide adducts include nitroglycerin, sodium nitroprusside, S-nitroso-proteins, S-nitroso-thiols, long carbon-chain lipophilic S-nitrosothiols, S-nitrosodithiols, iron-nitrosyl compounds, thionitrates, thionitrites, sydnonimines, furoxans, organic nitrates, and nitrosated amino acids, preferably mono- or poly-nitrosylated proteins, particularly polynitrosated albumin or polymers or aggregates thereof. The albumin is preferably human or bovine, including humanized bovine serum albumin. Such nitric oxide adducts are disclosed in U.S. Pat. No. 6,087,479 to Stamler et al. which is incorporated herein by reference.

In addition, biologically active materials include antiproliferative drugs such as steroids, vitamins, and restenosis-inhibiting agents. Preferred restenosis-inhibiting agents include microtubule stabilizing agents such as Taxol, paclitaxel, paclitaxel analogues, derivatives, and mixtures thereof. For example, derivatives suitable for use in the present invention include 2'-succinyl-taxol, 2'-succinyl-taxol triethanolamine, 2'-glutaryl-taxol, 2'-glutaryl-taxol triethanolamine salt, 2'-O-ester with N-(dimethylaminoethyl) glutamine, and 2'-O-ester with N-(dimethylaminoethyl) glutamide hydrochloride salt. Other preferred biologically active materials include nitroglycerin, nitrous oxides, nitric oxides, antibiotics, aspirins, digitalis, estrogen derivatives such as estradiol and glycosides. A biologically active material may be encapsulated in micro-capsules by the known methods.

5.3 Medical Devices with End Sections that Carry or Contain a Greater Amount of Biologically Active Material than the Middle Section

In another embodiment of the invention, a more uniform release-profile for a biologically active material along the length of the outer surface of the medical device may be achieved by preparing a medical device having end sections that carry or contain a greater amount of a biologically active material than the middle section.

In section 2, supra, the medical devices of the present invention having end sections that have increased capacity for carrying or containing a biologically active material were explained. When a coating composition comprising the biologically active material is applied to such medical devices by a conventional method, such as spraying, dipping, rolling, and electrostatic deposition, the end sections will carry or contain a greater amount of the biologically active material per unit length of the outer surface than the middle section of the outer surface.

However, greater amounts of biologically active material at the end sections can also be achieved by controlling the amount of the biologically active material that is applied to the middle and end sections. For instance, additional coating composition containing a biologically active material can be applied to the end sections so that such sections have a thicker coating and hence contain more biologically active material. A method for preparing such medical device comprises, for example, applying a first coating composition containing a biologically active material to the end sections and a middle section of an outer surface, placing a cover over the middle section, applying more of the first coating composition or second coating composition to the end sections of the outer surface. The second coating composition may contain the same biologically active material as the first coating composition having the same or different concentration or may contain a different biologically active material.

Another example of a method useful in allowing more biologically active material to the end sections relative to the middle section involves covering the middle section. In particular, a coating composition containing the desired biologically active material is applied to the middle section and end sections. The middle section is then covered by a sheath or mesh. Such covering can be achieved also by masking using photolithography techniques. Additional coating composition is then applied to the end sections. The covering prevents such additional coating composition from being applied to the middle section so that the end sections will contain relatively more biologically active material.

In yet another embodiment of the medical device of the present invention, a greater amount of the biologically active material can be applied to the end sections by applying coating compositions having different concentration of the first biologically active material to the middle and end sections. For example, applying a coating composition containing a first concentration of a biologically active material is applied to the end sections while the middle section is covered. Thereafter, a second coating composition having a second concentration of the biologically active material, which is smaller than the first concentration, to the middle section. The sections may be covered using sheaths or masking as explained above.

5.4 Medical Device Comprising a Biologically Active Material in a Radially Asymmetric Distribution

Yet another embodiment of the medical device of the invention achieves a greater amount of release of a biologically active material to a necessary body tissue. Such medical device comprises an outer surface comprising the biologically active material in a radially asymmetric distribution. For example, a rectangular portion of the outer surface has a greater amount of the biologically active material than the rest of the outer surface. When the medical device comprises a tubular portion, the rectangular portion may be parallel to longitudinal axis of the tubular portion. The rectangular portion may be the same length as that of the tubular portion. A greater amount of the biologically active material can be distributed to a rectangular portion using any of the manners used to distribute a greater amount of the biologically active material to the end sections (see section 5.3, supra).

6. Barrier Layer Over the Middle Section

In yet another embodiment, there is a barrier layer placed over the middle section of the outer surface, so that the end sections of the outer surface are allowed to release greater amounts of the biologically active material relative to the middle section. The middle and end sections are covered with a coating composition containing biologically active material. A covering or barrier layer is then placed over the middle section to limit the release of the biologically active material. In this way, the release ratio of biologically active material from the end sections is relatively greater than from the middle section.

Examples of such barrier layers include, but not limited to, a top-coating layer covering the middle section. When the medical device of the present invention is a stent, examples of such barrier layers include, but not limited to, a sheath with or without apertures or openings. Suitable material for making such barrier layer include, but not limited to, hydrophobic polymers listed in section 2.2, supra.

7. Expandable Stents Having Projecting Elements at their Ends

Another embodiment of the present invention is directed to an expandable stent, such as a balloon-expandable stent having two ends or edges and a tubular sidewall in between the ends. The tubular sidewall comprises a plurality of struts. The stent also comprises a plurality of projecting elements located at or proximate the ends or edges of the stent in its

unexpanded state. Each projecting element has two ends. One end of the projecting element is attached to or integral with a stent strut. When the stent is expanded to an expanded state, the end of the projecting element that is not attached to or integral with a stent strut defines the end or edge of the expanded stent. Also, the end of the unattached projecting element can define the end or edge of the stent in both its expanded and unexpanded state.

FIG. **21** shows an example of such a stent **210** in its unexpanded state. The stent **210** comprises two stent ends or edges **211***a* and **211***b* with a tubular sidewall **212** therebetween. The tubular sidewall **212** comprises or is made up of a plurality of struts **214**. In this stent **210** the struts **214** are arranged as a plurality of valleys **214***a* and apexes **214***b*. The sidewall comprises a plurality of projecting elements **215**, each having two ends **215***a* and **215***b*. The projecting elements are located proximate at least one stent end **211***a* and/or **211***b*. One end of the projecting element, e.g. a first projecting element end **215***a*, is attached to or integral with a stent strut **214**. Although this figure shows that the first projecting element end **215***a* is attached to or integral with a stent strut that forms a valley **214***a*, the first projecting element end **215***a* can be attached to or integral with a stent strut that forms an apex **214***b*.

FIG. **22** shows the stent **210** of FIG. **21** in its expanded state. When the stent **210** is expanded, or in an expanded state the projecting element ends **215***b* that are not attached to or integral with a stent strut (e.g. the second projecting element ends) are capable of defining at least one end or edge **211***a* and/or **211***b* of the stent **210**. Preferably the second projecting element ends **215***b* can define the stent end(s) **211***a* and/or **211***b* when the stent is in its fully expanded state; however the projecting element ends **215***b* can define the stent end(s) **211***a* and/or **211***b* when the stent is in a partially expanded state that is less than the fully expanded state.

The projecting elements **215** should have substantially no effect on the expansion of the stent. Moreover, the projecting elements do not radially expand when the stent is radially expanded. More specifically, with reference to FIGS. **21** and **22**, when the stent is radially expanded, apex **214***b* will radially expand and change in height or length from L to L', which is less than L. However, because of the configuration of the projecting element **215**, the projecting element will not expand in width w when the stent is expanded, i.e., the width w of the projecting element does not change or increase when the stent is radially expanded. Also, the projecting element does not change length when the stent is radially expanded. By not expanding in width when the stent expands, the projecting element acts as a source of stress relief.

Furthermore, the projecting elements **215**, shown in FIGS. **21** and **22** function as sources of stress relief because they are not supported at their sides as the apexes **214***b* are. The projecting elements are supported at only one print **215***c* (FIG. **22**) by a stent strut, i.e., the projecting element is attached or integral with a stent strut only at a single point of the projecting. In contrast the apexes are supported by stent struts at two points **215***c* and **215***d* (in FIG. **22**). The amount of support from adjacent struts can affect the strain at the end of a stent. Also, extension of the projecting elements **215** longitudinally beyond the apexes of the expanded stent act to relieve the strain. By extending further longitudinally toward the edge of the stent than the apexes, the projecting elements apply less force to the vessel than the apexes. This creates a region of lower stress between the apexes and native vessel beyond the end of the projecting elements.

Also, the projecting elements preferably lie along substantially the same plane as the struts of the stent. This way, at least a portion of each projecting element contacts a patient's lumen wall like the stent struts when the stent is placed in a body lumen. In embodiments of the expandable stent of the present invention, the projecting elements are preferably integral with the struts, namely, they are generally made from the same material as the struts and are formed as a continuous part of the struts. However, the struts and projecting elements can be made of different types of materials and are then connected or attached to each other. Preferably, the projecting elements and struts may be manufactured simultaneously; for example, struts having projecting elements can be laser-ablated from a plate of metal or polymer. In other embodiments the projecting elements may be attached to the stent struts after the stent is formed.

The projecting elements may be integral with or attached to struts at any portion proximate the ends of the unexpanded stent so long as the projecting elements do not hinder the stent from collapsing and expanding. When the struts are configured as a plurality of apexes and valleys, the projecting elements may be integral with or attached to struts at apexes, valleys or anywhere in between. For example, FIG. **21** shows a stent in its collapsed or unexpanded state, wherein the stent has projecting elements **215** integral with a strut forming a valley **214***a*. FIGS. **23-27***a* show ends of stents, wherein the projecting elements **230**, **240**, **250**, **260**, **260***a*, **270** and **270***a* are integral with or attached to struts forming apexes **214***b*. The projecting elements can be distributed uniformly or in any other manner proximate the ends of the stent.

The projecting elements suitable for the present invention may be in any shape including a straight rod, a bent rod, a rod having a greater width at the projecting elements free end (e.g., see FIGS. **22**, **23**, **24** and **27**), a rod having a hoop or circle or sphere at the free end (e.g., see FIGS. **26** and **26***a*), a truncated circle or cone (e.g., see FIG. **25**). Moreover, the projecting elements can have a serpentine-like or spiral-like shape as shown in FIG. **27***a*. Also, as shown, e.g., in FIG. **27**, the length of the projecting elements **270** may vary. Also, as shown in FIG. **27**, the free ends of the projecting elements not only define the ends of the stent in its expanded state but can also define the stent ends when the stent is in its unexpanded state.

The stent struts **214** may be fabricated from metallic and/or polymeric materials. Suitable metallic materials include metals and alloys based on titanium (such as nitinol, nickel titanium alloys, thermo-memory alloy materials), stainless steel, tantalum, nickel-chrome, or certain cobalt alloys including cobalt-chromium-nickel alloys such as Elgiloy® and Phynox®. Metallic materials also include clad composite filaments, such as those disclosed in WO 94/16646. Suitable polymeric materials include without limitation polyurethane and its copolymers, silicone and its copolymers, ethylene vinyl-acetate, polyethylene terephtalate, thermoplastic elastomers, polyvinyl chloride, polyolefins, cellulosics, polyamides, polyesters, polysulfones, polytetrafluorethylenes, polycarbonates, acrylonitrile butadiene styrene copolymers, acrylics, polylactic acid, polyglycolic acid, polycaprolactone, polylactic acid-polyethylene oxide copolymers, cellulose, collagens, and chitins.

The projecting elements suitable for the present invention may or may not comprise the same material as the stent struts. In some embodiments, it is preferable that the pro-

jecting elements are made from materials that are more flexible than the materials used to form the struts. When the projecting elements are more flexible than the struts, the strain exerted by the stent end against a body lumen, when the stent is in an expanded state, is reduced thereby reducing the possibility of restenosis that may occur at or near the implanted stent ends. More specifically, it has been hypothesized that the restenosis which can occur at or near the ends or edges of a stent implanted in a body lumen, may be caused by a lack of strain relief at or near the ends of the stent. It is believed that the stent struts at the ends of the stent exert too great a pressure against the body tissue that contacts the stent end. Therefore it is desirable to reduce the pressure exerted against the body tissue by the stent ends. The inclusion of projecting elements, whose free ends define the ends of the stent when the stent is in an expanded state, reduces the pressure or strain exerted by the ends of the expanded stent. One way that the use of projecting elements reduces such pressure or strain is by reducing the amount of stent material present at the ends of the expanded stent. Also, the projecting element may be configured in a shape more flexible than the struts, e.g., thinner and/or narrower than the struts. In this way, the projecting elements avoid the stress to be concentrated at the edges or ends of the stent and reduce the "edge effect."

As shown in FIG. **22**, by including projecting elements **215**, the stent end **211***b*, which is defined by the free end or second end of the projecting elements **215***b*, is located at line a-a. If the projecting elements **215** were not included as a part of the stent the end of the expanded stent would be located at line b-b. As can be seen in FIG. **22**, the amount of stent material at line a-a is less than at line b-b. Thus, inclusion of the projecting elements also reduces the amount of stent material at the stent ends, thereby reducing the pressure exerted by the stent ends against the body tissue. In addition to the amount of stent material, as discussed above, the amount of support from adjacent struts as well as the thickness of the strut impact the strain at the end of a stent.

Furthermore, making the projecting element from materials that are more flexible than the materials used to make the stent struts also reduces the pressure exerted by the ends of an expanded stent against body tissue. The use of more flexible material for the projecting elements, whose free end defines the end(s) of the expanded stent, allows the stent to have more "give", thereby reducing the pressure the stent end exerts against body tissue when the stent is implanted in a body lumen.

In a preferred embodiment, at least one strut and/or at least one projecting element comprises a biologically active material. Suitable biologically active materials are discussed above in Section 5.2. The strut or projecting element can be coated with the biologically active material. The coating can further include polymeric materials. Suitable polymeric materials are set forth above in Section 5.1. Alternatively, the biologically active material can be incorporated into the materials used to form the struts or projecting elements such as a polymer having a biologically active material incorporated therein. Moreover, as shown in FIGS. **23** and **24** the projecting elements **230** and **240** can be the shape of a rod having an end with a greater width at the second projecting end and at least one depression or indentation **231** and **241**, respectively which contains the biologically active material **232**. The depressions can also include a polymeric material in addition to the biologically active material. The indentations can be in the shape of cavities that can extend partly or entirely through the projecting element.

In another embodiment, as shown, e.g., in FIGS. **28** and **29** the projecting elements **280** have openings **281**. FIG. **28** shows stent end **211***b* when the stent is unexpanded. FIG. **29** shows the stent end **211***b* when the stent is expanded. A ribbon **282** can be passed or threaded through the openings **281**. The ribbon **282** contains a biologically active material. The ribbon may or may not be elastic as long as it does not substantially hinder the stent from expanding. The ribbon may be a tape and/or a fabric comprising a polymeric material. Suitable polymeric materials for making the ribbon include without limitation polyurethane and its copolymers, silicone and its copolymers, ethylene vinyl-acetate, polyethylene terephtalate, thermoplastic elastomers, polyvinyl chloride, polyolefins, cellulosics, polyamides, polyesters, polysulfones, polytetrafluorethylenes, polycarbonates, acrylonitrile butadiene styrene copolymers, acrylics, polylactic acid, polyglycolic acid, polycaprolactone, polylactic acid-polyethlyene oxide copolymers, cellulose, collagens, and chitins. In some embodiments, the biologically active material is coated on the ribbon. The coating can be applied onto the ribbon in any method, for example, dipping, spraying, electrostatic deposition and rolling. In other embodiments, the ribbon is prepared by soaking a fabric ribbon in a biologically active material solution. In addition, the struts and/or projecting elements can include a biologically active material, such as a coating comprising a biologically active material.

The description contained herein is for purposes of illustration and not for purposes of limitation. Changes and modifications may be made to the embodiments of the description and still be within the scope of the invention. Furthermore, obvious changes, modifications or variations will occur to those skilled in the art. Also, all references cited above are incorporated herein, in their entirety, for all purposes related to this disclosure.

We claim:

**1**. An expandable stent comprising two ends and a tubular sidewall between the two ends,

wherein the sidewall comprises a plurality of struts, and a plurality of projecting elements located proximate at least one stent end;

wherein each projecting element comprises a first projecting element end and a second projecting element end;

wherein the first projecting element end is integral with or attached to a strut;

wherein the second projecting element end is capable of defining at least one stent end when the stent is in an expanded position;

wherein at least one of the struts or at least one of the projecting elements comprises a biologically active material, wherein the biologically active material comprises an antiproliferative agent; and

wherein at least one projecting element is configured in a shape of a rod having an end with a greater width at the second projecting element end, and at least one indentation for containing the biologically active material located at the second projecting element end.

**2**. The stent of claim **1**, wherein the projecting element is configured such that the projecting element does not expand in width when the stent is radially expanded.

**3**. The stent of claim **1**, wherein all of the struts and all of the projecting elements comprise the biologically active material.

**4**. The stent of claim **1**, wherein the strut or projecting element that comprises the biologically active material comprises a coating containing the biologically active material.

5. The stent of claim 4, wherein the coating further comprises a polymeric material.

6. The stent of claim 1, wherein the biologically active material is sirolimus or everolimus.

7. The stent of claim 1, wherein the biologically active material is paclitaxel, a derivative of paclitaxel or an analog of paclitaxel.

8. The stent of claim 1, wherein the struts and the projecting elements comprise the same material.

9. The stent of claim 1, wherein the struts comprise a first material and the projecting elements comprise a second material.

10. The stent of claim 1, wherein the struts are configured as a plurality of apexes and valleys, and wherein the projecting elements are integral with or attached to at least one of the valleys.

11. The stent of claim 1, wherein the projecting elements are distributed uniformly at the ends of the stent.

12. The stent of claim 1, wherein the struts are configured as a plurality of apexes and valleys, and wherein the projecting elements are integral with or attached to at least one of the apexes.

13. The stent of claim 9, wherein the second material is more flexible than the first material.

14. The stent of claim 1, wherein the stent is a balloon expandable stent.

15. An expandable stent comprising two ends and a tubular sidewall between the two ends,

wherein the sidewall comprises a plurality of struts, and a plurality of projecting elements located proximate at least one stent end;

wherein each projecting element comprises a first projecting element end and a second projecting element end;

wherein the first projecting element end is integral with or attached to a strut;

wherein the second projecting element end is capable of defining at least one stent end when the stent is in an expanded position;

wherein at least one of the struts or at least one of the projecting elements comprises a biologically active material, wherein the biologically active material comprises an antiproliferative agent; and

wherein at least some of the projecting elements comprise an opening therein and wherein the stent further comprises a ribbon comprising the biologically active material, and wherein the ribbon passes through at least one of the openings in the projecting elements.

16. The stent of claim 15, wherein the projecting element is configured such that the projecting element does not expand in width when the stent is radially expanded.

17. The stent of claim 15, wherein all of the struts and all of the projecting elements comprise the biologically active material.

18. The stent of claim 15, wherein the strut or projecting element that comprises the biologically active material comprises a coating containing the biologically active material.

19. The stent of claim 18, wherein the coating further comprises a polymeric material.

20. The stent of claim 15, wherein the biologically active material is sirolimus or everolimus.

21. The stent of claim 15, wherein the biologically active material is paclitaxel, a derivative of paclitaxel or an analog of paclitaxel.

22. The stent of claim 15, wherein the struts and the projecting elements comprise the same material.

23. The stent of claim 15, wherein the struts comprise a first material and the projecting elements comprise a second material.

24. The stent of claim 23, wherein the second material is more flexible than the first material.

25. The stent of claim 15, wherein the struts are configured as a plurality of apexes and valleys, and wherein the projecting elements are integral with or attached to at least one of the valleys.

26. The stent of claim 15, wherein the projecting elements are distributed uniformly at the ends of the stent.

27. The stent of claim 15, wherein the struts are configured as a plurality of apexes and valleys, and wherein the projecting elements are integral with or attached to at least one of the apexes.

28. The stent of claim 15, wherein the stent is a balloon expandable stent.

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